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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: May 21, 2003

SUBJECT: PP#: 2F2609. **Human Health Risk Assessment for the Section 3 Use of Hydramethylnon in/on Pineapple.** PC Code: 118401. DP Barcode: D228934. Submission: S509968

FROM: William D. Cutchin, Chemist
Science Information Management Branch (SIMB)
Health Effects Division (HED) (7509C)

and

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Registration Action Branch 2 (RAB2)/HED (7509C)

THRU: Richard Loranger, Branch Senior Scientist
RAB2/HED (7509C)

TO: S. Moats/ R. Keigwin
Insecticide Rodenticide Branch
Registration Division (7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed use of hydramethylnon [tetrahydro- 5,5-dimethyl -2(1H) -pyrimidinone (3-(4-(trifluoromethyl) phenyl)-1-(2-(4-(trifluoromethyl)phenyl)ethenyl)-2-propenylidene) hydrazone] on pineapples

A summary of the findings and an assessment of human risk resulting from the registered and proposed tolerances for hydramethylnon is provided in this document. The risk assessment, the residue chemistry data review, and the dietary risk assessment were provided by William Cutchin (SIMB), the hazard characterization by John Whalan (RAB2), the occupational/residential exposure assessment by Gary Bangs (RAB2), and the drinking water assessment by Santhini Ramasamy of the Environmental Fate and Effects Division (EFED).

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Recommendation for Tolerances
The residue chemistry and toxicological databases support the requested tolerance of 0.05 ppm for hydramethylnon on pineapples. The Agency has also previously recommended that the grass forage tolerance be increased to 2.0 ppm and the grass hay tolerance be increased to 0.1 ppm (Hydramethylnon RED, EPA 738-R-98-023, 12/98).

Memoranda used in support of this risk assessment:

Hydramethylnon - Report of the Hazard Identification Assessment Review Committee, TXR# 0051786, J. Whalan, 4/9/03.
Occupational and Residential Exposure and Risk Assessment For Hydramethylnon, DP Barcode: D288800, G. Bangs, 5/20/03.
Hydramethylnon. PP 2F2609. Request for the Use on Pineapple. Summary of Analytical Chemistry and Residue Data, DP Barcode: D287763, W. Cutchin, 4/1/03.
Hydramethylnon Acute and Chronic Dietary Exposure Assessments for the Section 3 Registration of Pineapple, PP#2F2609, DP Barcode: D288910, W. Cutchin, 3/31/03, & DP Barcode: D289833, W. Cutchin, 5/7/03.
Section 3 New Crop Use Registration of Hydramethylnon on Pineapples in Hawaii for Control of Bigheaded Ants, DP Barcode: D249596, S. Ramasamy, 3/19/03.
Hydramethylnon Reregistration Eligibility Decision, EPA 738-R-98-023, December 1998.

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1.0 EXECUTIVE SUMMARY

Hydramethylnon is a slow-acting insecticide of the amidinohydrazone chemical class registered for the control of ants (big-headed, fire, and harvester) in pastures, rangelands, and other noncrop lands such as lawns, turfs, and non-bearing nursery stocks. It is also registered for the control of household ants and cockroaches in nonfood use areas in domestic dwellings and commercial establishments.

BASF Corp. has submitted a petition for the registration of hydramethylnon for use on pineapples. The proposed registration is an amendment to the following currently registered product: AMDRO® Granular (EPA Reg No. 421-322) formulated as a bait intended for broadcast or direct application to ant mounds.

According to the OPP Reference Files System (REFS), there are currently 30 registered products containing hydramethylnon. Hydramethylnon formulations are of the general form of granulated baits and gels. For outdoor use, products are either broadcast or sprinkled directly onto pest mounds with application timing and frequency dependant on pest infestation. For indoor use, the products are formulated into self contained bait traps (child resistant packaging) or gels for crack and crevice use.

The most recent HED human health risk assessment was conducted in conjunction with the Hydramethylnon RED (EPA 738-R-98-023, December 1998). Since the completion of this risk assessment, the following has occurred: 1) a revisit to HED Hazard Identification Assessment Review Committee (HIARC) on March 4, 2003, where an acute oral toxicity endpoint for females 13-50 yrs old was selected and 2) in accordance with the February 2002 OPP 10x guidance document, a re-evaluation of the FQPA Safety Factor (SF).

Hazard Assessment
A complete toxicity data base has been provided for hydramethylnon. Oral toxicity has been well characterized in the rat, mouse, rabbit, and dog. The only dermal toxicity study, an unacceptable 21-day dermal toxicity study in rabbits, showed no systemic toxicity at the highest dose tested. Although hydramethylnon toxicity has not been characterized by the inhalation route, this route of exposure is unlikely to pose a hazard because hydramethylnon has a low vapor pressure, and because of the way it is formulated and applied. The Acute Toxicity Categories for the technical are **III** for oral and dermal toxicity and for eye irritation; and **IV** for inhalation toxicity and skin irritation. Hydramethylnon is not a dermal sensitizer.

The testes were clearly the primary target organ in rats, mice, dogs, and rabbits, and the consequence of this was manifest as impaired reproductive performance in the reproductive toxicity study in rats and in the dominant lethal study in rats. The latter study demonstrated a slow reversibility of these effects. Although there is no evidence of endocrine involvement, it remains a possibility.

A steep dose response was seen in several studies. A comparison of subchronic and chronic studies demonstrates a modest degree of toxicity cumulation. There was no evidence of increased quantitative or qualitative susceptibility in the rat or rabbit fetuses in the developmental toxicity studies. There was no sign of neurotoxicity in any study.

On 3/28/91 the Agency's Cancer Peer Review Committee (CPRC) determined that hydramethylnon should be classified as a "Group C" carcinogen, a possible human carcinogen, and recommended that, for the purpose of risk characterization, the Reference Dose approach should be used for quantification of human risk (March 28, 1991). The Agency's HIARC (3/4/03) confirmed the recommendation that the RfD approach be used, i.e., that a quantitative dietary cancer risk assessment is not required. Dietary risk concerns due to long-term consumption of hydramethylnon residues are adequately addressed (protective) by the chronic exposure analysis using the RfD.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision
As mentioned previously, the HED HIARC met on 3/4/03 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to hydramethylnon according to the February 2002 OPP 10x guidance document. This was a re-evaluation of the toxicology database subsequent to the evaluation by the Toxicology Endpoint Selection Committee (TES) dated 7/2/97 and revised 9/23/97 (HED DOC. NO. 013446). The HIARC has no concern or residual uncertainties for pre- and/or post-natal toxicity, and no concern for developmental neurotoxicity. Therefore, the HIARC recommended that an additional database uncertainty factor was not needed for hydramethylnon (3/4/03; TXR # 0051786). The special FQPA SF was reduced to 1x based the conservative residue assumptions used in the dietary and residential exposure risk assessments, and the completeness of the residue chemistry and environmental fate databases (evaluated by the risk assessment team).

The acute RfD (aRfD) for females 13-50 yrs old was calculated by dividing the No-Observed-Adverse-Effect-Level (NOAEL) by 100 (10x for interspecies extrapolation, 10x for intraspecies variation). The cRfD was calculated by dividing the NOAEL by 100 (10x for interspecies extrapolation, 10x for intraspecies variation). Since the special FQPA SF has been reduced to 1x, the acute and chronic population adjusted doses (aPAD and cPAD) are equal to the aRfD and cRfD, respectively. Considering that exposure is to the hydramethylnon granular product containing $\leq 1\%$ active ingredient, and that dermal absorption is estimated to be less than 1%, dermal bioavailability would generally be too low to be of concern. Inhalation exposure is generally not of concern because hydramethylnon has a low vapor pressure (2.03×10^{-8} mm Hg), and because granular, gel, and bait formulations are not extensively inhalable. However, because there are endpoints of concern for dermal and inhalation exposure routes and surrogate chemical data are used for the exposure estimates, dermal and inhalation exposure and risk estimates will be conducted. The levels of concern for occupational and residential exposures by all routes are for margins of exposure (MOEs) <100. Oral, dermal and inhalation exposure estimates can be aggregated because similar effects are expected regardless of exposure pathway.

Endpoints used for risk assessment purposes are summarized below.

Exposure Scenario	Dose	Endpoint	Study/Effect
Acute dietary Females 13-50 yr Gen. Population	NOAEL = 5 mg/kg/day NA	aRfD and aPAD = 0.05 mg/kg/day NA	Developmental toxicity in rabbits - abortions NA
Chronic dietary	Oral NOAEL = 1.66 mg/kg/day	cRfD and cPAD = 0.017 mg/kg/day	2-Generation reproductive toxicity in rats - testicular effects
Incidental Oral (all durations)	Oral NOAEL = 1.66 mg/kg/day	Target MOE = 100 (residential)	
Dermal (all durations)	Oral NOAEL = 1.66 mg/kg/day (1% dermal absorption rate)	Target MOE = 100 (occupational and residential)	2-Generation reproductive toxicity in rats - testicular effects.
Inhalation (all durations)	Oral NOAEL = 1.66 mg/kg/day		

Residential Exposure Estimates

HED has conducted a non-dietary exposure and risk assessment for hydramethylnon including the following uses: residential consumers applying granular and gel formulations; children and adults contacting recreational turf or residential lawns treated with hydramethylnon; and toddlers' incidental nondietary ingestion of products applied around the home. Non-occupational handler exposures from the granular formulations applied to outdoor residential sites are assumed to be short-term in duration, based on rapid dissipation and insect foraging.

No chemical-specific data were submitted for the registration of hydramethylnon uses. Per HED policy, non-occupational handler assessments are based on surrogate unit exposures from the draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (12/18/97) and recommended approaches by HED's Exposure Science Advisory Committee (ExpoSAC). Updates to the Residential SOPs (02/01) alter the residential postapplication scenario assumptions. These updated assumptions are expected to better represent residential exposure and are still considered to be high-end, screening level assumptions. The non-occupational handler assessments for push type granular spreaders were based on surrogate unit exposures from two Outdoor Residential Exposure Task Force (ORETF) studies.

The ant bait stations containing hydramethylnon are in child-resistant packaging (CRP). The bait stations are supposed to be placed in less accessible locations such as in or under kitchen counters. However, handling or mouthing of the bait stations is the most commonly reported incidental "exposure" to hydramethylnon. "There were nearly 1,000 cases of exposure to hydramethylnon baits reported to Poison Control Centers in 1989 in children under age six. Over 200 of these cases received follow-up and no symptoms of any kind were reported in over 95% of the exposures. Where symptoms were reported they were minor and of the type that did not require special medical attention. This suggests that nearly all exposures involve, at most,

children mouthing the bait container with little or no contact with the actual bait" (DP Barcode: D231127, Rereg. Case: 2585, J. Blondell, 8/27/97). The bait station should be normally considered an article and accidental exposure to the internal contents of bait stations would not be expected. HED acknowledges that the CRP is not child proof. If a child were to open and ingest the contents of an entire bait station , there is no acute dietary endpoint for children which could be used to calculate an acute risk. However, using the subchronic endpoint dose of 1.7 mg/kg/day, a child consuming a bait trap containing 21 mg of active ingredient would result in a MOE slightly greater than 1. In order to attain an MOE of 100, no more than 4 mg ai should be ingested by a 15 kg child (19% of one bait station).

The gel product containing hydramethylnon is supposed to be applied in dime-sized portions in locations inaccessible to children. Accidental ingestion of gel from such application is considered unlikely and was therefore not assessed.

Adult consumer exposures when installing and removing child-resistant packaged bait stations are expected to be minimal. Consumer exposure when applying the gel compound from a syringe is considered negligible. There were no applicable data to estimate such an exposure. However, comparison to the application of granular bait by hand may characterize the magnitude of exposure, as the percent active ingredient are similar. For the proposed application of granules to outdoor residential sites, dermal MOEs calculated for non-occupational handlers were all 10,000 or greater. Limited accessibility (i.e., crack, crevice, behind appliances, in crawl spaces) of the gel and granular formulations when used by professional applicators in the home make it unlikely that residents would be exposed to these formulations indoors.

Dermal postapplication exposure from lawns treated with hydramethylnon granules at the maximum application rate of 2.2 lb product per acre (0.022 lb ai/A) were estimated using standard assumptions, as no chemical-specific residue data were available. For adults and children playing actively for two hours on a just-treated lawn, the estimated MOEs were 41,000 and 24,000, respectively. The aggregate (dermal, hand-mouth and object-mouth) MOE for a 15 kg child playing on a lawn was 4000. The MOE for incidental ingestion of 3 mg of 1% hydramethylnon granules found on the surface of the lawn was 850. The precise size range of granules for the proposed formulation is not known, although they are described as small, as they are supposed to be movable by ants. Because the granules are relatively small, and dispersed sparingly or directly on ant mounds, they are less likely to be noticed by a child, then ingestion is less likely. The likelihood of dermal contact is also reduced.

It is suggested that all labels specifically state what measures should be taken to prevent accidental postapplication exposure to hydramethylnon granular or gel bait formulations. For example, spills should be promptly cleaned up, empty used containers discarded immediately after use, and open partially full containers should be placed in a sealed plastic bag. All labels should emphasize prompt hand washing with soap and water (necessary due to oily formulation) after use.

Residue Exposure Estimates

There are hydramethylnon tolerances on grass and grass hay following treatment of pasture and rangeland at 0.05 ppm established in terms of parent only, tetrahydro- 5,5-dimethyl -2(1H) -pyrimidinone (3-(4-(trifluoromethyl) phenyl)-1- (2-(4-(trifluoromethyl)phenyl)ethenyl) -2-propenylidene) hydrazone. The Metabolism Assessment Review Committee (MARC) determined that the residue of concern in grasses and the milk, meat, and meat byproducts of ruminants is hydramethylnon *per se* and that there is no reasonable expectation of finite hydramethylnon residues of concern in the milk, meat, and meat byproducts of ruminants [40 CFR §180.6(a)(3)] as a result of hydramethylnon use on grasses. Since there are no detectable hydramethylnon residues in the pineapple feed item, process residues, tolerances for hydramethylnon residues in animal commodities need not be established.

The method used for data collection, designated M 2458, is the predecessor to method M 2458.01 for which the petitioner has submitted an independent method validation. Analysis is conducted by HPLC-UV using an octadecasilane column. The limits of quantitation (LOQ) are 0.01 ppm for juice and 0.05 ppm for other pineapple matrices. The limit of detection (LOD) for all pineapple matrices is 0.005 ppm. For the proposed pineapple use the product, formulated as AMDRO® Granular (EPA Reg No. 421-322), is applied six times by ground broadcast equipment with a 30-day PHI with application timing and frequency dependant on pest infestation. Field trial data provided in support of the requested new use indicated that no detectable residues of hydramethylnon were found in any pineapple RAC or processed commodity (<0.005 ppm) even when the product was applied at 5x the proposed rate.

Dietary Exposure Estimates

Acute and chronic dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™; ver. 1.30) program which incorporates consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996/1998. For acute and chronic dietary risk estimates, HED's level of concern is for estimates that exceed 100% aPAD or cPAD, respectively.

A Tier 1 (conservative, deterministic assessment using tolerance-level residues, 100% crop treated (CT) for the proposed commodity; and DEEM-FCID™; ver. 1.30) acute dietary exposure assessment was conducted for the female 13-50 yrs old population subgroup. In addition, since processing information indicated that hydramethylnon residues were not expected to concentrate in pineapple processed commodities, processing factors set to 1. The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for the female 13-50 population subgroup (<1% of the aPAD). The acute assessment was highly conservative, using several upper-end assumptions. Inclusion of anticipated residues (ARs) and % CT data could be made in order to refine the acute dietary assessment.

A Tier 1 (conservative, deterministic assessment using tolerance-level residues, and 100% crop treated (CT) for the proposed commodity; and DEEM-FCID™; ver. 1.30) chronic dietary

exposure assessment was conducted for the general U.S. population and various population subgroups. In addition, since processing information indicated that hydramethylnon residues were not expected to concentrate in pineapple processed commodities, processing factors set to 1. The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (<1% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-6 years old, at <1% (0.2%) of the cPAD. The chronic assessment was conservative, using several upper-end assumptions. Additional refinements, such as inclusion of ARs and % CT information could be made in order to refine the chronic dietary assessment.

Drinking Water Exposure Estimates

Per the recommendations of the HED Metabolism Assessment Review Committee (MARC), EFED provided drinking water estimated environmental concentration (EECs) for hydramethylnon only. The Tier I model, FIRST (FQPA Index Reservoir Screening Tool, version 1.0, Aug 1, 2001) was used to estimate drinking water concentrations of hydramethylnon in surface water. This model predicts the peak and annual average concentrations of the pesticide in drinking water from surface water sources. The peak concentration is used to estimate acute risks from exposure of humans to hydramethylnon in drinking water from surface water sources. The annual average concentration is used to estimate chronic risks from exposure of humans to hydramethylnon in drinking water from surface water sources.

Ground water contamination is expected to be low due to high binding affinity of hydramethylnon to the soil. For any potential ground water contamination from the proposed use of hydramethylnon on pineapples, SCI-GROW (version 2.2, Nov 1, 2001) modeling was performed. The model estimates the upper bound ground water concentrations of pesticides likely to occur when the pesticide is used at the maximum allowable rate in areas where a shallow ground water table is particularly vulnerable to contamination. The SCI-GROW model is based on the fate properties of the pesticide, the application rate, and the number of applications. The resultant value is appropriate for estimating acute and chronic risks for the human health dietary risk assessment.

For surface water, the acute (peak) and chronic (annual average) EECs are 76.09 ppb and 1.45 ppb, respectively. The acute and chronic ground water EEC is 0.035 ppb.

Aggregate Exposure Scenarios and Risk Conclusions

For the proposed uses, human health aggregate risk assessments have been conducted for the following exposure scenarios: acute aggregate exposure (food + drinking water), short-term aggregate exposure (food + drinking water + residential), and chronic aggregate exposure (food + drinking water). Since the short-and intermediate-term endpoints are the same, an intermediate-term aggregate risk assessment was not performed because the short-term exposure assessment would be the worst-case to assess both exposure durations. A separate cancer aggregate risk assessment was not performed based on the recommendation that the RfD approach be used. All EEC values are less than the lowest drinking water level of comparison (DWLOC) values of 1500

ppb, 144 ppb, and 170 ppb determined for the acute, short-term, and chronic scenarios, respectively. Therefore, the EECs do not exceed HED's level of concern. **All aggregate exposure and risk estimates do not exceed HED's level of concern for the scenarios listed above.**

Occupational Exposure Estimates
HED has conducted a non-dietary exposure and risk assessment for hydramethylnon including the following uses: occupational handlers applying granular formulations; and postapplication workers entering fields treated with hydramethylnon granules.

The short- and intermediate-term endpoints for dermal and inhalation exposures to hydramethylnon are based on the same study, have the same endpoint effect, and therefore, the absorbed daily doses can be combined. However, it is not necessary to calculate the intermediate-term exposure since, using the same dose to estimate risk, the short-term estimates represent the most conservative MOEs.

No chemical-specific data were submitted for the registration of hydramethylnon uses. As per HED policy, most occupational handler assessments are based on surrogate unit exposures from the Pesticide Handler Exposure Database (PHED) as presented in the PHED Surrogate Exposure Guide (8/98). The occupational handler assessments for push type granular spreaders were based on surrogate unit exposures from two Outdoor Residential Exposure Task Force (ORETF) studies.

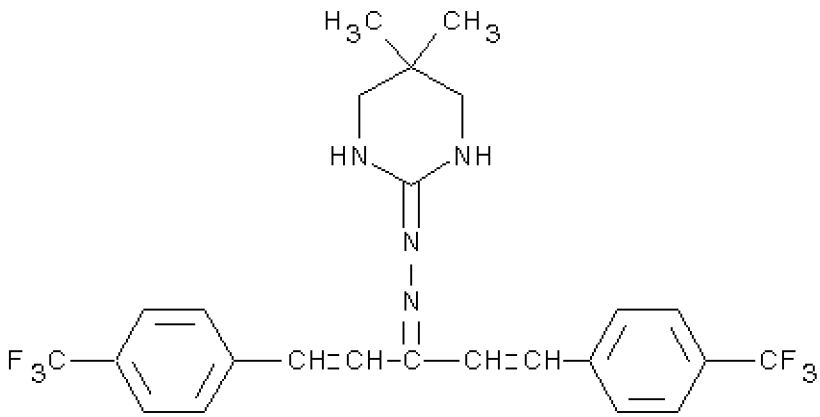
Granular formulations containing hydramethylnon may be applied to pineapples up to six times per year at the lowest label rate. Occupational handler exposures from the granular formulations applied to outdoor agricultural sites are assumed to be short-term (1 to 30 days) in duration. The short/intermediate-term MOEs calculated for agricultural handlers and flaggers ranged from 9500 to over 100,000 without gloves. For hand dispersal with gloves, the MOE was 220,000; and aerial applicators in closed cockpit planes had MOEs of 13,000.

Reentry workers will likely be exposed to very little hydramethylnon, if the granular bait functions to attract the target pests and the pests take the bait to their nest as intended. Assuming the maximum label rate application, there were no reentry worker risk estimates of concern even at reentry day zero (0), or just after application. Pineapple workers' risk estimates ranged from MOEs of 30,000 to 100,000, although these estimates do not consider that they typically wear gloves to prevent injury from the plant leaves.

Recommendations for Tolerances
The residue chemistry and toxicological databases support the establishment of the proposed hydramethylnon tolerance of 0.05 ppm in/on pineapples. The Agency has previously recommended that the grass forage tolerance be increased to 2.0 ppm and the grass hay tolerance be increased to 0.1 ppm (Hydramethylnon RED, EPA 738-R-98-023, 12/98).

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Active Ingredient

TABLE 1. Hydramethylnon Nomenclature	
Compound	 Chemical Structure
Common name	hydramethylnon
Company experimental name	CL 217300
IUPAC name	5,5-dimethylperhydropyrimidin-2-one 4-trifluoromethyl-αa-(4-trifluoromethylstyryl)cinnamylidenehydrazone
CAS name	tetrahydro-5,5-dimethyl-2(1H)-pyrimidinone [3-[4-(trifluoromethyl)phenyl]-1-[2-[4-trifluoromethyl)phenyl]ethenyl]-2-propenylidene]hydrazone
CAS #	67485-29-4
Molecular Weight	494.5
End-use product/EP	AMDRO® Granulated Insecticide, 0.73 % ai (EPA Reg. No. 241-322)

2.2 Physical and Chemical Properties

TABLE 2. Physicochemical Properties	
Parameter	Value
Melting point/range	185-190 °C
pH	NA
Density	15-24 lbs/ft^3 (bulk formula)

TABLE 2. Physicochemical Properties	
Parameter	Value
Water solubility (25 °C)	0.88 ppm
Solvent solubility (g/L at 20 °C)	acetone 360, ethanol 72, 1,2-dichloroethane 170, methanol 230, isopropanol 12, xylene 94, chlorobenzene 390
Vapor pressure at 25 °C	2.03×10^{-8} mm Hg
Dissociation constant (pK_a)	NA
Octanol/water partition coefficient $Log(K_{OW})$	2.31
UV/visible absorption spectrum	NA

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for hydramethylnon supports the establishment of permanent tolerances for residues of hydramethylnon in/on the RACs resulting from the proposed uses.

3.1 Hazard Profile

Toxicity Data Base Overview:

A complete toxicity data base has been provided for hydramethylnon. Oral toxicity has been well characterized in the rat, mouse, rabbit, and dog. The only dermal toxicity study, an unacceptable 21-day dermal toxicity study in rabbits, showed no systemic toxicity at the highest dose tested. Although hydramethylnon toxicity has not been characterized by the inhalation route, this route is unlikely to pose a hazard because hydramethylnon has a low vapor pressure and because of the way it is formulated and applied. The carcinogenicity studies in mice and rats are adequate for cancer classification.

The testes were clearly the primary target organ in rats, mice, dogs, and rabbits, and the consequence of this was manifest as impaired reproductive performance in the reproductive toxicity study in rats and in the dominant lethal study in rats. The latter study demonstrated a slow reversibility of these effects. There was evidence of a steep dose response in several studies, most notably in the 91-day gavage study in dogs and in the reproductive toxicity study.

Acute Toxicity:

The Acute Toxicity Categories for the technical are **III** for oral and dermal toxicity and for eye irritation; and **IV** for inhalation toxicity and skin irritation. Hydramethylnon is not a dermal sensitizer.

Subacute and Subchronic Toxicity:

No systemic toxicity was observed in a 21-day dermal toxicity study in rabbits at the highest dose tested–250 mg/kg/day (one-fourth of the limit dose). This study is unacceptable because the vehicle was unknown, half of the animals had abraded skin, and skin lesions were observed in the controls.

The most sensitive endpoints in a subchronic feeding study in rats were decreased testicular weights (↓34%) and testicular atrophy. Significant decreases in body weight gain and food consumption occurred at higher doses.

In dogs, testicular atrophy and decreased testicular weights were observed in a 91-day study, but not in a 26 week study (probably because the high dose was too low). A steep dose response was seen in the 91-day study where 3 mg/kg/day was a NOAEL and 6 mg/kg/day was a lethal level. Additional clinical signs seen in the 91-day study include decreased food consumption and body weight gain, cachexia, elevated ALT, and wasting of muscle and subcutaneous fat. In the 26 week study, common findings included soft stools, mucoid stools, and diarrhea.

Developmental and Reproductive Toxicity:

There was no evidence of increased quantitative or qualitative susceptibility in the rat or rabbit fetuses in the developmental toxicity studies. For each species, the maternal and developmental LOAELs were the same. In the rats, effects seen at the Maternal LOAEL included a 16% decrease in body weight, increased incidence of nasal mucus, alopecia, soft stools, staining of the ano-genital fur, yellowish discoloration of the fat, and small thymus. Effects seen at the Developmental LOAEL included decreased mean fetal weights and increased incidence of rudimentary structures and incompletely ossified supraoccipitals.

In the rabbits, effects seen at the Maternal LOAEL included abortions (3 litters), soft stools, reduced amount of stools, and anogenital matting and discharge. Effects seen at the Developmental LOAEL were abortions and a 16% decrease in fetal weights.

In a two-generation reproductive toxicity study in rats, the LOAEL was based on microscopic lesions including degeneration of the germinal epithelium (1/29) and aspermia (1/29). Decreased reproductive performance in the high-dose was manifest as longer precoital intervals and lower impregnation rates for the males; and reduced gestation weight gain and smaller litters in females. There was a steep dose response between the minimal findings at 3.32 mg/kg/day and frank toxicity at 5.05 mg/kg/day. There was no evidence of systemic toxicity or direct toxicity in the offspring.

Mutagenicity:

Negative mutagenic findings were seen in 1.) an Ames Assay in *Salmonella typhimurium* and

Escherichia coli, 2.) a forward gene mutation assay in *Schizosaccharomyces pombe*, 3.) an *in vitro* cytogenetic assay in Chinese hamster ovary (CHO) cells, 4.) a rat dominant lethal assay, and 5.) a *Saccharomyces cerevisiae* D4 mitotic gene conversion assay. The findings of adverse effects on spermatocytes and/or spermatogonia in the dominant lethal assay are consistent with the results of the 2-generation reproduction study in rats showing that hydramethylnon is a reproductive toxicant which appears to specifically target the germinal cells and/or tissues in the testes.

Chronic Toxicity/Carcinogenicity:

In a chronic feeding/carcinogenicity study in Charles River CD rats, no compound-related clinical signs were observed and survival was not affected by treatment. The LOAEL was based on small, soft testes, decreased testicular weights (27%), and testicular atrophy in males; and decreased body weight gain in females (22%). Statistically significant findings of neoplasia were found in the uterus (adenomatous polyps) and adrenals (medullary adenomas), but these were not considered toxicologically significant because they were seen at doses above the MTD.

In an 18 month carcinogenicity feeding study in Charles River CD-1 mice, survival decreased as the dose increased, but not enough to jeopardize the study. The LOAEL was based on testicular degeneration (hypospermia, interstitial cell hyperplasia of Leydig cells, and germinal cell degeneration) in males, and combined lung adenomas and carcinomas in females. Findings of hyperplasia and neoplasia in the lungs of males were not considered toxicologically significant because they were seen at doses above the MTD. Findings in females of statistically significant increases in lung adenomas and combined lung adenomas/carcinomas were, however, considered toxicologically significant.

The Cancer Peer Review Committee classified hydramethylnon as a Group C—possible human carcinogen, and recommended that, for the purpose of risk characterization, the Reference Dose approach should be used for quantification of human risk. This classification was based upon statistically significant increases in lung adenomas and combined lung adenomas/carcinomas in female mice. The Cancer Peer Review report was issued on March 28, 1991 (TXR: 0008350). On March 4, 2003, the HIARC concurred with the cancer classification.

Neurotoxicity:

There was no evidence of neurotoxicity in any studies.

Endocrinopathy:

Decreased reproductive performance, including longer precoital intervals and lower pregnancy rates, was seen in the reproductive toxicity study at the dose above the LOAEL. The fact that several studies report microscopic lesions in the testes and epididymides clearly shows that these are target organs. Although there is no evidence of endocrine involvement, it remains a

possibility.

Metabolism and Pharmacokinetics:

In a metabolism study in male and female Sprague-Dawley rats, the majority of administered phenyl- or pyrimidinyl- ^{14}C-hydramethylnon was recovered in the feces (85-98%). Recovery in the urine was minimal (1-2% of the administered dose). There were no sex or dose-related differences in urinary or fecal elimination. Radiolabel retention in the tissues was somewhat greater in the females. Distribution of the residues retained by all tissues accounted for <10% of the administered dose, with most of the radiolabeled material accumulating in the carcass. Most of the radioactivity (94-99%) in the feces was unchanged parent compound. In contrast, the urine contained traces of parent compound and polar metabolites which may be benzoate, cinnamate, or pyrimidinone derivates. Polar metabolites in the tissue were probably ketone, pyrimidinone, cinnamate, and benzoate derivatives.

Dermal Absorption

Although there are no dermal absorption studies of technical hydramethylnon, two studies were performed in Sprague-Dawley rats using low percentage gel formulations. The total absorbed dose after 10 hours of exposure was 0.414% for 2% a.i. Maxforce Gel®, and 0.97% for 2.16% a.i. Siege®.

Toxicology Profile

Table 3 presents the acute toxicity of hydramethylnon. Table 4 describes the status of the hydramethylnon data base and the findings for each study.

Table 3. Acute Toxicity Profile of Hydramethylnon Technical

OPPTS No./Study Type	MRID	Results
870.1100 Acute Oral - Rat American Cyanamid Co. Study A90-117 July 19, 1990	41612503	**LD_{50} = 817 mg/kg (♂); 1502 mg/kg (♀), 1146 mg/kg (♂ + ♀)** Clinical signs: Decreased activity, diuresis, anorexia, ataxia, epistaxis, chromodacryorrhea, salivation, and emaciation. **Toxicity Category III** **Guideline**
870.1200 Acute Dermal - Rabbit American Cyanamid Co. Study A90-114 July 1, 1993	41612504	**LD_{50} >2000 mg/kg (limit test)** There was no evidence of toxicity. **Toxicity Category III** **Minimum**

Table 3. Acute Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.1300 Acute Inhalation - Rat Bio/Dynamics Inc. Study 91-8399 July 16, 1993	42871101	**LC_{50} = 3.1 mg/L (♂), 3.4 mg/L (♀), 2.9 mg/L (♂ + ♀)**; 4-hour analytical, whole body exposure; MMAD (GSD) = 2.0 µm (2.8). Clinical signs: Labored breathing, gasping, eye closure, decreased activity, rales, excessive salivation, yellow material on the fur, and decreased weight gain. **Toxicity Category IV** **Acceptable**
870.2400 Primary Eye Irritation - Rabbit American Cyanamid Co. Study A90-140 August 22, 1990	41612505	Corneal opacity and conjunctival redness, chemosis, and discharge reversed within 7 days. Hydramethylnon is a moderate irritant. **Toxicity Category III** **Guideline**
870.2500 Primary Skin Irritation - Rabbit American Cyanamid Co. Study A90-95 June 21, 1990	41612506	There was no evidence of dermal irritation or systemic toxicity. **Toxicity Category IV** **Guideline**
870.2600 Dermal Sensitization - Guinea Pig Food and Drug Research Laboratories Study 7180 May 5, 1982	101560	Not a dermal sensitizer **Minimum**

Table 4. Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3100 Subchronic Feeding - Rat Pharmacopathics Research Laboratories Study 7866 May 31, 1979	32641	**NOAEL = 2.5 mg/kg/day** **LOAEL = 5.0 mg/kg/day** - decreased testicular weights (34%), and testicular atrophy. Clinical signs: None Clinical pathology: Negative Gross lesions: None Microscopic pathology: Testicular atrophy Levels tested: 0, 50, 100, 200, or 400 ppm (0, 2.5, 5.0, 10.0, or 20.0 mg/kg/day). **The sponsor chose to lower the dose for the 400 ppm group to 25 ppm [sic] on day 15 due to significant decreases in body weight gain and food consumption.** **Acceptable**
870.3100 Subchronic Feeding - Mice	–	–

Table 4. Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3150 Subchronic Gavage - Dog Pharmacopathics Research Laboratories Study 7864 May 31, 1979	61794	**NOAEL = 3 mg/kg/day** - LDT; decreased food consumption (11% / 20%, ♂/♀) and body weight gain (11% / 9%, ♂/♀). **LOAEL = [not defined]** **Lethal Dose = 6 mg/kg/day** - decreased food consumption and body weight gain, ↑SGPT, cachexia, wasting of muscle and subcutaneous fat, testicular atrophy, and death. Three males and three females dosed at 6.0 mg/kg/day died or were sacrificed moribund between days 27 and 75, and all high-dose dogs were sacrificed moribund between days 27 and 53. The mid and high-dose dogs began refusing their feed after week 2. Body weights in the low, mid, and high-dose groups were decreased as much as 11%, 51%, and 34% in males; and 9%, 42%, and 37% in the females (body weight decreases were greatest in the mid-dose dogs because they survived longer than the high-dose dogs). Clinical signs: Cachexia at necropsy (mid and high-dose) Clinical pathology: SGPT increased 4-8 fold in surviving mid-dose females at 2 months. Microscopic pathology: wasting of muscle and subcutaneous fat, and testicular atrophy in the mid and high-dose dogs. Levels tested: 0, 3.0, 6.0, or 12.0 mg/kg/day via capsule for 91 days. **Acceptable**
870.3150 Subchronic Gavage - Dog Hazleton Laboratories Study 362-156 June 10, 1980	92163037	**NOAEL = 1.0 mg/kg/day** **LOAEL = 3.0 mg/kg/day** - increased incidence of soft stools, mucoid stools, and diarrhea. No dogs died in this study. Clinical signs: Increase in the incidence of soft stools, mucoid stools, and diarrhea in high-dose dogs. A high-dose male was removed from the study due to anorexia between study days 42 and 98, and 120 to termination. Food consumption, body weights, clinical pathology, ophthalmologic examinations, and histopathology were normal. Gross pathology: Half of the high-dose dogs had yellow-tinged body fat, but this was not considered to be a toxic effect. Levels tested: 0, 0.33, 1.0, and 3.0 mg/kg/day via capsule for 26 weeks. The control group received 120 mg/kg/day of lactose. **Acceptable**
870.3200 21-Day Dermal - Rabbit Hazleton Raltech, Inc. Study 80033 April 15, 1982	101559	**NOAEL = 250 mg/kg/day (HDT)** Food consumption was depressed as much as 38% and 45% in the high-dose males and females, compared to controls. The high-dose males and females weighed as much as 8% and 9% less than the controls. The platelet count in the high-dose females at termination was 54% less than controls, but was not considered adverse because it is a common finding following skin abrasion. Levels tested: 0, 10, 50, or 250 mg/kg/day on clipped skin of dorsal trunk. Half of each group was abraded prior to treatment. **Unacceptable**

Table 4. Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.3465 13-Week Inhalation	–	–
870.3700 Developmental Toxicity - Rat Bio/Dynamics Inc. Study 79-2382 September 14, 1979	92163038	**Maternal NOEL = 3 mg/kg/day** **Maternal NOAEL = 10 mg/kg/day** - 8% decrease in body weight and yellowish discoloration of the fat. **Maternal LOAEL = 30 mg/kg/day** - 16% decrease in body weight; increased incidence of nasal mucus, alopecia, soft stools, staining of the ano-genital fur, yellowish discoloration of the fat, and small thymus. **Developmental NOEL = 10 mg/kg/day** **Developmental LOAEL = 30 mg/kg/day** - decreased mean fetal weights and increased incidence of rudimentary structures and incompletely ossified supraoccipitals. At 30 mg/kg/day, a 16% decrease in maternal body weight, increased incidence of clinical signs (nasal mucus, alopecia, soft stool, staining of anogenital fur), yellowish discoloration of the fat, and small thymus were observed. Levels tested: 0, 3, 10, or 30 mg/kg/day on gestation days 6-15. Vehicle controls were dosed with corn oil. **Acceptable**
870.3700 Developmental Toxicity - Rabbit International Research & Development Corp. Study 141-024 April 7, 1982	101558	**Maternal NOAEL = 5 mg/kg/day** - soft stools, and reduced amount of stools. **Maternal LOAEL = 10 mg/kg/day** - abortions, soft stools, reduced amount of stools, and anogenital matting and discharge. **Developmental NOAEL = 5 mg/kg/day** - decreased fetal weight (8%). **Developmental LOAEL = 10 mg/kg/day** - abortions, decreased fetal weight (16%). Two high-dose does died during the post-treatment period of undermined causes. Three mid-dose and three high-dose does aborted. Levels tested: 0, 5, 10, or 20 mg/kg/day on gestation days 6-18. Vehicle controls were dosed with corn oil. **Acceptable**
870.3800 2-Generation Reproductive Toxicity - Rat Pharmaco - LSR Ltd. Study 92-4026 July 19, 1995	43741501	**Reproductive/Systemic NOAEL = 25 ppm (1.66 / 2.01 mg/kg/day, ♂/♀)** **Reproductive/Systemic LOAEL = 50 ppm (3.32 / 4.13 mg/kg/day, ♂/♀)** (degeneration of the germinal epithelium (1/29) and aspermia (1/29) There was no evidence of systemic toxicity, or direct toxicity in the offspring. Reproductive effects seen at 75 ppm included decreased reproductive performance in males manifest as longer precoital intervals and lower pregnancy rates; and reduced gestation weight gain and smaller litters in females. Levels tested: 0, 2, 50, or 75 ppm (0, 1.66, 3.32, or 5.05 mg/kg/day in males; 0, 2.02, 4.13, or 6.19 mg/kg/day in females) in diet. **Acceptable**

Table 4. Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.4100 Chronic Feeding Toxicity - Dog	–	See 870.3150
870.4200 Carcinogenicity Feeding - Mouse (18 months) International Research & Development Corp. Study 141-013 May 6, 1982	101563	**NOAEL = 25 ppm (3.57 mg/kg/day) in males** **NOAEL = not defined in females.** **LOAEL = 50 ppm (6.93 mg/kg/day) in males** (testicular lesions) **LOAEL = 25 ppm (4.45 mg/kg/day) in females** (LDT; combined lung adenomas and carcinomas) The high-dose females were sacrificed after 5 weeks due to high mortality. Survival @18 months at the 50 and 100 ppm doses was 72% and 46% in males, and 66% and 46% in females, respectively. Survival in controls was 86% in males and 76% in females. Gross lesions: None Microscopic lesions: Testicular degeneration in the 50, 100, and 200 ppm males (hypospermia, interstitial cell hyperplasia of Leydig cells, and germinal cell degeneration); and amylodosis in the kidneys of the 50 and 100 ppm females. CARC defined the MTD as being between 50 ppm and 100 ppm in both sexes, and concluded that mouse mortality and other effects support 50 ppm as an acceptable dose to adequately assess potential carcinogenic effects. Hyperplasia and neoplasia in the lungs of males was not considered toxicologically significant because they were seen above the MTD. Increases in lung adenomas in females at 50 and 100 ppm (27% and 27%, respectively) and combined lung adenomas/carcinomas at 25, 50, and 100 ppm were considered toxicologically significant. Levels tested: 0, 25, 50, 100, or 200 ppm (0, 3.57, 6.93, 14.2, and 28.6 mg/kg/day in males, and 0, 4.45, 6.87, 17.3, and 33.1 mg/kg/day in females) in diet. **Acceptable**
870.4300 Chronic Feeding Toxicity/Carcinogenicity-Rat International Research and Development Corporation Study 141-014 May 12, 1982	101565	**NOAEL = 50 ppm (2.4 mg/kg/day in ♂, 3.0 mg/kg/day in ♀)** **LOAEL = 100 ppm (4.9 mg/kg/day in ♂, 6.2 mg/kg/day in ♀)** (small, soft testes, decreased testicular weights (↓27%), and testicular atrophy in males; decreased body weight gain in females) The MTD was 100 ppm in males and 50 ppm in females based on significant decreases in body weight at higher doses. Statistically significant findings of neoplasia were found in the uterus (adenomatous polyps) and adrenals (medullary adenomas), but these were not considered toxicologically significant because they were seen at doses above the MTD. Levels tested: 0, 25, 50, 100, or 200 ppm (0, 1.2, 2.4, 4.9, or 10.0 mg/kg/day in males; 0, 1.5, 3.0, 6.2, or 12.1 mg/kg/day in females) in feed. **Acceptable**

Table 4. Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.5100 Bacterial Reverse Mutation Test (Ames Assay) BASF Corporation Study GTOX 1982	42132701	Negative up to an insoluble dose (1000 µg/plate with or without S9 activation) in *S. typhimurium* TA1535, TA1537, TA98 and TA100 and *E. coli* WP2 uvrA.
870.5375 *In Vitro* Chromosomal Aberration in Chinese Hamster Ovary (CHO) Cells Litton Bionetics, Inc. Study 20990 October 1, 1985	40422401	Negative up to a cytotoxic dose (500 ng/mL -/+S9)
870.5450 Rodent Dominant Lethal Assay - Rat American Cyanamid Company Study 79163 June 24, 1980	35897	Negative in male rats administered 3 or 30 mg/kg of CL 217,300 once daily for 5 days by oral gavage. The highest assayed dose (90 mg/kg) caused a decrease in fertility at mating week 6 and 100% infertility at mating week 7. Fifty percent of the high-dose males regained fertility by week 17 (120 days after treatment had ceased). At necropsy (week 17), 80% of the high-dose group had smaller testes and epididymides. There was, however, no indication of a dominant lethal effect at any dose. Overall, these findings suggest an adverse effect on spermatocytes and/or spermatogonia. **Minimum**
870.5575 D4 Mitotic Gene Conversion Assay Life Science Research Study 129006-M-07685 January 14, 1986	40407602	Negative in *Saccharomyces cerevisiae* up to the highest dose tested (25 µg/plate +/-S9).
P1 Forward Gene Mutation Assay	40407603	Negative in *Schizosaccharomyces pombe* up to the highest assayed levels (12.5 µg/mL -S9; 50 µg/mL +S9).
870.6200 Acute Neurotoxicity - Rats	–	–
870.6200 Feeding Subchronic Neurotoxicity - Rats	–	–

Table 4. Toxicity Profile of Hydramethylnon Technical		
OPPTS No./Study Type	**MRID**	**Results**
870.7485 Metabolism - Rat Xenobiotic Laboratories, Inc. Study XBL 90043 May 2, 1992	42448902	The majority of the administered dose of phenyl- or pyrimidinyl-^{14}C-Cl 217,300 was recovered in the feces (85-98%). Recovery in the urine was minimal (1-2% of the administered dose). There were no sex or dose-related differences in urinary or fecal elimination. Radiolabel retention in the tissues was somewhat greater in the females. Distribution of the residues retained by all tissues accounted for <10% of the administered dose, with most of the radio labeled material accumulating in the carcass. Most of the radioactivity (94-99%) in the feces was unchanged parent compound. In contrast, the urine contained traces of parent compound and polar metabolites which may be benzoate, cinnamate, or pyrimidinone derivates. Polar metabolites in the tissue were probably ketone, pyrimidinone, cinnamate, and benzoate derivatives. Levels tested: Groups of male and female Sprague-Dawley rats were dosed by gavage with Amdro (CL 217,300) labeled with ^{14}C in either the phenyl or pyrimidinyl ring. Rats received either a single low-dose (3 mg/kg), a single high-dose (100 mg/kg), or 14 consecutive doses of 2 mg/kg/day unlabeled test material followed by a single 2 mg/kg dose with the ^{14}C in either ring. **Acceptable**
870.7600 Dermal Penetration - Rat Bushy Run Research Center Study 92N1073 October 13, 1993	42989101	Sprague-Dawley rats were dermally dosed with a gel formulation containing 2% a.i. (Maxforce Gel®). Total dose absorbed after 10 hours was 0.414% **Acceptable**
870.7600 Dermal Penetration - Rat Hazleton Wisconsin, Inc. Study HWI/6123/180 1993	43093901	Sprague-Dawley rats were dermally dosed with a gel formulation containing 2.16% a.i. (Siege®). Total dose absorbed after 10 hours was 0.97% **Acceptable**

3.2 FQPA Considerations

The HIARC considers the toxicology database for hydramethylnon to be complete and adequate for the evaluation of risks to infants and children. Available studies include developmental studies in two species and a multi-generation reproduction study. The HIARC concluded that there are no indications of neurotoxicity in the available data that would suggest a need for neurotoxicity or developmental neurotoxicity studies.

There was no evidence of increased quantitative or qualitative susceptibility in rat or rabbit fetuses following *in utero* exposures or following pre- and/or post-natal exposure in the two generation reproduction study.

In the rats, effects seen at the Maternal LOAEL of 30 mg/kg/day included an 16% decrease in body weight; increased incidence of nasal mucus, alopecia, soft stool, and staining of the ano-

genital fur; and yellowish discoloration of the fat and small thymus. Effects seen at the Developmental LOAEL of 30 mg/kg/day included decreased mean fetal weights and increased incidence of rudimentary structures and incompletely ossified supraoccipitals.

In the rabbits, effects seen at the Maternal LOAEL of 10 mg/kg/day included abortions (3 litters), soft stools, reduced amount of stools, and anogenital matting and discharge. Effects seen at the Developmental LOAEL of 10 mg/kg/day included abortions (3 litters) and a 16% decrease in fetal weight which was probably due to decreased food consumption in the does.

In the two generation reproduction study, no offspring toxicity was seen at the highest dose tested.

The HIARC has no concern or residual uncertainties for pre- and/or post-natal toxicity, and no concern for developmental neurotoxicity. There is no evidence that hydramethylnon is neurotoxic or that the developing fetus or the young animal is qualitatively or quantitatively more susceptible to hydramethylnon.

The HIARC determined that no special FQPA Safety Factor is needed (1x) for hydramethylnon based on toxicity.

The hydramethylnon risk assessment team evaluated the quality of the exposure data and based on those data recommended that the Special FQPA Safety Factor be reduced to 1x. The recommendation is based on the following:

- The *acute* and *chronic* dietary food exposure assessment utilizes existing and proposed tolerance level residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated

- The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

- The residential uses for hydramethylnon were calculated using Residential SOPs, which are considered to represent high-end screening assumptions.

3.3 Dose-Response Assessment

On March 4, 2003, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) selected the doses and toxicological endpoints summarized in Table 5 for use in risk assessments. Also included in this table is the FQPA Safety Factor (SF) selected by the HIARC. This table is followed by the HIARC's rationales for selection of endpoints and doses, aggregation guidance, and cancer classification.

Table 5. Doses and Toxicological Endpoints for Hydramethylnon			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-50 years of age)	NOAEL = **5** mg/kg/day UF = **100** **Acute RfD** = **0.05** mg/kg/day	FQPA SF = **1** **aPAD** = acute RfD / FQPA SF = **0.05** mg/kg/day	Developmental toxicity in rabbits LOAEL = **10** mg/kg/day based on abortions.
Acute Dietary (General population including infants and children)	–	–	There is no appropriate single dose endpoint for the general population.
Chronic Dietary (All populations)	NOAEL= **1.66** mg/kg/day UF = **100** **Chronic RfD** = **0.017** mg/kg/day	FQPA SF = **1** **cPAD** = chronic RfD / FQPA SF = **0.017** mg/kg/day	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.
Short-Term Incidental Oral (1-30 days)	NOAEL= **1.66** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.
Intermediate-Term Incidental Oral (1-6 months)	NOAEL= **1.66** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.
Short-Term Dermal (1 to 30 days)	Oral NOAEL= **1.66** mg/kg/day (dermal absorption rate = **1** %)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.
Intermediate-Term Dermal (1 to 6 months)	Oral NOAEL= **1.66** mg/kg/day (dermal absorption rate = **1** %)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.
Long-Term Dermal (>6 months)	Oral NOAEL= **1.66** mg/kg/day (dermal absorption rate = **1** %)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.

Table 5. Doses and Toxicological Endpoints for Hydramethylnon			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (all durations)	Oral NOAEL= **1.66** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	2-Generation reproductive toxicity in rats LOAEL = **3.32** mg/kg/day based on testicular effects.
Cancer (oral, dermal, inhalation)	The Cancer Peer Review Committee determined that hydramethylnon should be classified as a Group C—possible human carcinogen, and recommended that, for the purpose of risk characterization, the Reference Dose approach should be used for quantification of human risk. The Cancer Peer Review report was issued on March 28, 1991. The HIARC concurred with the cancer classification on March 4, 2003.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

Acute Reference Dose (aRfD)- Females 13-50 Years

The endpoint seen after the *in utero* exposure is relevant for this population of concern and is presumed to occur after a single exposure.

Acute Reference Dose (aRfD) - General Population

An appropriate endpoint attributable to a single dose was not available for this population subgroup in the data base including the developmental toxicity studies.

Chronic Reference Dose (cRfD)

Testicular effects are the critical effect of concern in the 2 generation reproductive toxicity study and in other studies of hydramethylnon.

Occupational/Residential Exposure

Incidental Oral Exposure: Short-Term (1-30 days)

Testicular effects are the critical effect of concern in this and other studies of hydramethylnon. The use of this study for this exposure period (short-term) was judged to be appropriate because the onset of testicular effects are unknown, and this dose would be protective of these effects in the population of concern (infants and children).

Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

This dose/endpoint/study is appropriate for the population (infants and children), duration (intermediate-term), and effects of concern (testicular).

Dermal Exposure: All Durations

Testicular effects are the critical effect of concern in this and in other studies of hydramethylnon. This endpoint and uncertainty factor should be protective of potential testicular effects which are of unknown time of onset. The 21-day dermal toxicity study (MRID 00101559) was deemed unacceptable because the vehicle was unknown, half the animals had abraded skin, and skin lesions were observed in the control animals. Since an oral dose was selected, a 1% dermal absorption factor should be used for route-to-route extrapolation.

Inhalation Exposure: All Durations

There are currently no expectations of inhalation exposure during actual conditions of use. Testicular effects are the critical effect of concern in this and in other studies of hydramethylnon. This endpoint and uncertainty factor should be protective of potential testicular effects which are of unknown time of onset, assuming an oral:inhalation absorption ratio of 1, no portal-of-entry effects, and equivalent toxicity by the oral and inhalation routes. There are no multiple exposure inhalation toxicity studies for hydramethylnon.

Recommendation for Aggregate Exposure Risk Assessments

For short, intermediate, and long-term aggregate exposure risk assessments, the oral, dermal, and inhalation routes can be combined since oral equivalents were selected for the dermal and inhalation routes of exposure.

Cancer (oral, dermal, inhalation)

The Cancer Peer Review Committee classified hydramethylnon as a Group C—possible human carcinogen, and recommended that, for the purpose of risk characterization, the Reference Dose approach should be used for quantification of human risk. This classification was based upon statistically significant increases in lung adenomas and combined lung adenomas/carcinomas in female mice. The Cancer Peer Review report was issued on March 28, 1991 (TXR No. 0008350). The HIARC concurred with the cancer classification.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, hydramethylnon may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

Hydramethylnon is a slow-acting stomach poison insecticide used to control imported fire ants, harvester ants, big-headed ants, and cockroaches indoors; on agricultural crops, pastures, and rangeland; ornamental and shade trees; ornamental herbaceous plants; and ornamental lawns and turf. In addition, hydramethylnon has been used in sewage systems to coat the backs of manhole covers. Agency data show that approximately 95% of the chemical's limited usage in pounds per active ingredient is in non-agricultural use, such as homeowner bait use and professional pest control application. About 5% of the total amount used may be in agriculture, primarily on pastures and rangeland. Hydramethylnon is applied in bait boxes or by ground, air, or by hand. The maximum application rate, formulated as a granular bait, is 0.0176 lb a.i./A.

There are 30 registered products that contain hydramethylnon as the a.i. Hydramethylnon is the active ingredient in the end use products *Amdro*, *Combat*, *Maxforce*, *Sensible*, and *Siege*. These products are used primarily to control ants in grasses and rangelands and other non-crop lands such as lawns, turf, and non-bearing nursery stock. Hydramethylnon is also registered for the control of household ant species and cockroaches in nonfood use areas in and around domestic dwellings and commercial establishments. The registered granular formulation may be applied via broadcast or individual mound treatment for imported fire ant control. For the control of ants and cockroaches in dwellings, the gel formulation may be applied as a bait or as a crack and crevice treatment.

The proposed new use is an amendment to the currently registered product: AMDRO® Granular

(EPA Reg No. 421-322) formulated as a bait intended for broadcast or direct application to ant mounds. Hydramethylnon is being proposed for use on pineapples. The product may be applied up to six times at 0.0073 lb a.i./A to a maximum total of 0.044 lb a.i./A/season with a 30-day PHI. Maximum single-use rate for high infestations is 0.022 lb a.i./A. The petitioner has provided an end-use product label including the proposed hydramethylnon use directions [i.e., maximum use rates (single) and preharvest intervals (PHIs)] for all the commodities associated with this risk assessment. The proposed use patterns are acceptable and are supported by the available residue data.

Table 6. Summary of Proposed Use Pattern for Hydramethylnon.

PP/ID#	Use/ Commodity	Proposed Formulation	PHI (days)	Max. #App. /season	Maximum Application Rate (lb.ai/A)		RTI (days)	Restrictions
					per app.(at 3 lb prod/A)	per season		
2F2609	Pineapple	AMDRO Granular	30	6	0.022	0.044	60	Foliar applications.

4.2 Dietary Exposure/Risk Pathway

The residue chemistry data submitted in support of proposed petitions were reviewed in the HED-memoranda: "Request for the Use on Pineapple. Summary of Analytical Chemistry and Residue Data" (PP#2F2609, DP Barcode: D287763, W. Cutchin, 4/1/03). The drinking water assessment was completed by EFED on 3/19/03 (S. Ramasamy, DP Barcode: D249596). The acute and chronic dietary exposure assessment was completed in a HED memorandum dated 3/31/03 (W. Cutchin, DP Barcode: D288910). A residential exposure assessment for hydramethylnon was prepared in an HED memorandum dated in process (G. Bangs, DP Barcode: D288800).

4.2.1 Residue Profile

Background
BASF Corp. has submitted a petition to register the use of hydramethylnon on pineapple. The petitioner is proposing the establishment of permanent tolerances for the residues of hydramethylnon in/on pineapple at 0.05 ppm.

Existing tolerances of 0.05 ppm are currently established for the insecticide hydramethylnon in or on grasses, forage (pasture and rangeland) and grasses, hay (pasture and rangeland), respectively (40 CFR §180.395(a)). The Agency no longer distinguishes between rangeland and pastures and has recommended that the grass forage tolerance be increased to 2.0 ppm and the grass hay tolerance be increased to 0.1 ppm (DP Barcode: D239231, D. Hrdy, 9/24/97). These tolerances

have been corrected due to a change to a zero day (0-day) post harvest interval (PHI) and that the Agency no longer allows a PHI restriction for use on grass. A Section 18 Emergency Exemption tolerance with expiration/revocation dates are established in/on pineapples under 40 CFR §180.395(b). No indirect or inadvertent tolerances are established as a result of application of the pesticide to growing crops and other non-food crops.

There are no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for hydramethylnon.

Nature of the Residue in Plants

The HED Metabolism Committee on 1/25/96 concluded that hydramethylnon, *per se*, is the residue to be regulated on grasses (MARC, TXR: 0051219, DP Barcode: D221981, 2/22/96). The majority of the radioactive residue in grasses was identified as parent. Hydramethylnon is metabolized very rapidly via cleavage of the hydrazone bond to form the ketone analog: 1,5-bis (α,α,α-trifluoro-*p*-tolyl)-1,4-pentadien-3-one (CL 98724), then rapidly degraded to produce: α,α,α-trifluoro-*p*-toluic acid (CL 71640) and/or trifluoromethylcinnamic acid (CL 243236) most likely due to hydrolysis or photodecomposition products which retain the aromatic system and at least one benzylic moiety.

For pineapple, studies indicate that the parent compound is extensively metabolized in pineapple to a variety of organo and water soluble metabolites. Additionally, at the exaggerated rate of 20x the proposed use rate, the maximum TRR in fruit was 0.03 ppm. The parent metabolizes rapidly in pineapple via hydrolysis at the hydrazone bond to form a ketone derivative, CL 98724, and the hydrazine, CL 85646. This is followed by further oxidation of the ketone to produce CL 243236 and CL 71640. The methyl esters of the two acids are also observed. These and most other polar metabolites are likely hydrolysis or photodecomposition products which retain the aromatic ring and at least one benzylic moiety. The major residues included parent, CL 71640, CL 243236, CL 98724, CL 243049, CL 243049-Me, CL 247176, and CL 85646. Structures of parent and metabolites are listed in Attachment 1.

The nature of the residue of hydramethylnon in plant commodities has been adequately determined for the current and proposed uses. However, there are not sufficient studies to determine the nature of the residues on all RACs. Should the registrant request uses on other commodities, further metabolism studies will be required.

Nature of the Residue in Livestock

An acceptable ruminant metabolism study has been submitted and evaluated (MRID: 42871102, DP Barcode: D194154, CBRS#: 12,402, S. Knizner, 1/26/94). The terminal residue to be regulated in the milk, meat, and meat byproducts of ruminants is hydramethylnon *per s*e. The MARC previously determined that there is no reasonable expectation of finite hydramethylnon residues of concern in the milk, meat, and meat byproducts of ruminants [40 CFR §180.6(a)(3)] as a result of hydramethylnon use on grasses (MARC, TXR: 0051219, DP Barcode: D221981, 2/22/96). The Agency has recommended that the grass forage tolerance be increased to 2.0 ppm

and the grass hay tolerance be increased to 0.1 ppm and no change in the 40 CFR §180.6(a)(3) status for ruminant commodities was indicated (Hydramethylnon RED, EPA 738-R-98-023, 12/98). A poultry metabolism study is not required at this time because there are no poultry feed items associated with the current and proposed uses.

Residue Analytical Methods

Adequate enforcement methods are available for determination of hydramethylnon residues in plants. The method used for data collection in pineapples, M 2458.01, has been submitted as an independent method validation (PP#2F2609, MRID 4082302, DP Barcode: D287763, W. Cutchin, in process). Residues from pineapple matrices are extracted using acidic water:acetone. The samples are filtered through a Buchner funnel lined with glass fiber filter. The samples are then concentrated using a rotary evaporator and redissolved in methanol. The samples are acidified and loaded onto a C-18 filter cartridge. After successive washes, the analyte is eluted with acidic methanol, concentrated again using a rotary evaporator and redissolved in water:acetonitrile. Analysis is conducted by HPLC-UV using an octadecasilane column. The limits of quantitation (LOQ) are 0.01 ppm for juice and 0.05 ppm for other pineapple matrices. The limit of detection (LOD) is 0.005 ppm.

The Pesticide Analytical Manual (PAM) Vol. II lists a gas liquid chromatography method with electron capture detection (GLC/ECD) for the analysis of hydramethylnon residues in/on grass commodities (Pesticide Reg. Sec180.395). The PAM Vol. II method, designated as Method I, has a detection limit of 0.05 ppm. The Agency has forwarded to FDA a confirmatory high pressure liquid chromatography (HPLC) method (American Cyanamid Method M2334) for inclusion in PAM Vol. II as a lettered method. Method M2334 determines residues of hydramethylnon *per se* in/on grass commodities, and has a detection limit of 0.05 ppm. Method M2334 has undergone successful independent laboratory validation (DP Barcode: D215252, MRID 43632801, CBRS No. 15570, D. Hrdy, 10/10/95) and been forwarded for Agency validation to ACL/BEAD.

Multiresidue Method (MRM)

The FDA PESTDATA database of January 1994 (PAM Volume I, Appendix I) indicates that recovery of hydramethylnon using multi-residue methods is unlikely.

Magnitude of Residues in Plants

Existing tolerances of 0.05 ppm are currently established for the insecticide hydramethylnon in or on grasses, forage (pasture and rangeland) and grasses, hay (pasture and rangeland), respectively (40 CFR §180.395). The Agency no longer distinguishes between rangeland and pastures. The Agency has recommended that the grass forage tolerance be increased to 2.0 ppm and the grass hay tolerance be increased to 0.1 ppm (DP Barcode: D239231, D. Hrdy, 9/24/97). These tolerances have been corrected due to a change to a zero day (0-day) post harvest interval (PHI) and that the Agency no longer allows a PHI restriction for use on grass.

Crop field trials were conducted Hawaii in pineapples at 1x and 5x the proposed annual

application rate with pre-harvest intervals (PHI) of 29 or 30 days. The results from these trials show that maximum residues of hydramethylnon on pineapples are below the limit of detection (<0.005 ppm) with a 30-day PHI at 1x or 5x the proposed application rate.

Magnitude of Residues in Processed Commodities
Hydramethylnon was applied to pineapples at 1x and 5x the proposed annual application rate with a pre-harvest interval (PHI) of 29 days. The whole pineapples were processed into slices, beverage juice, ion exchange juice (IONEX juice), bran, and waste pulp. The 1x and 5x treated whole pineapple RAC had no detectable hydramethylnon residues. After processing, none of the processed commodities had detectable residues of hydramethylnon.

Magnitude of Residues in Meat, Milk, Poultry and Eggs (MMPE)
The MARC (MARC, TXR: 0051219, DP Barcode: D221981, 2/22/96) has determined that from the currently registered uses there are no reasonable expectations of finite hydramethylnon residues of concern in milk, meat, and meat byproducts of ruminants [40 CFR §180.6(a)(3)]. The Agency has recommended that the grass forage tolerance be increased to 2.0 ppm and the grass hay tolerance be increased to 0.1 ppm, however no change in the 40 CFR §180.6(a)(3) status for ruminant commodities was indicated (Hydramethylnon RED, EPA 738-R-98-023, 12/98). Since the were no detectable residues in pineapple processed commodities even at 5x the proposed treatment rate, no residues in meat or milk are expected from the feeding of those commodities to animals. A poultry feeding study is not required at this time because there are no poultry feed items associated with grasses or pineapple.

Confined and Field Accumulation in Rotational Crops
Pineapples and grasses grown in pastures are typically not rotated. Therefore, no rotational residue chemistry data are required.

4.2.2 Dietary Exposure Analyses

Hydramethylnon acute and chronic dietary exposure were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a

deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

The results of the acute and chronic assessments are listed in Table 7. DEEM-FCID™ (Ver. 1.30) estimates the dietary exposure for the U.S. population and 28 population subgroups. Based on an analysis of 1994-96, 98 CSFII consumption data which took into account dietary patterns and number of survey respondents, HED determined that the following population groupings were appropriate for regulatory purposes (only the exposure estimates for these populations are reported in this document): U.S. Population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, females 13-49 years old, adults 20-49 years old, and/or adults 50+ years old.

4.2.2.1 Acute Dietary Exposure Analysis

An unrefined, Tier 1 acute dietary exposure assessment was conducted using tolerance-level residues and assuming 100% CT for all registered and proposed commodities. The acute analysis was conducted for females 13-49 years old only as no appropriate single dose endpoint was established for the general U.S. population and infants and children.

The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for females 13-49 years old (<1% of the aPAD) and all other population subgroups. The acute assessment was highly conservative, using several upper-end assumptions. ARs and %CT data could be used in order to refine the acute assessment.

4.2.2.2 Chronic Dietary Exposure Analysis

An unrefined, Tier 1 acute dietary exposure assessment was conducted for the general U.S. population and various population subgroups. Tolerance-level residues and assuming 100% CT was used for all registered and proposed commodities

The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (<1% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at <1% (0.02%) of the cPAD. The chronic assessment was conservative, using upper-end assumptions. Additional refinements, such as inclusion of ARs and % CT data, could be made in order to refine the chronic assessment.

Table 7. Summary of Dietary Exposure and Risk for Hydramethylnon

Population Subgroup	Acute Dietary[1]		Chronic Dietary[2]		Cancer Dietary
	Dietary Exposure (mg/kg/day)	%aPAD	Dietary Exposure (mg/kg/day)	%cPAD	
U.S. Population	NA	NA	0.000005	<1	NA[3]
All Infants (<1 year old)			0.000012	<1	
Children 1-2 years old			0.000026	<1	
Children 3-5 years old			0.000016	<1	
Children 6-12 years old			0.000008	<1	
Youth 13-19 years old			0.000002	<1	
Adults 20-50 years old			0.000003	<1	
Females 13-50 years old	0.000004	<1	0.000004	<1	
Adults 50+ years old	NA	NA	0.000002	<1	

1. Acute dietary endpoint of 0.05 mg/kg/day applies to females 13-49 only.
2. Chronic dietary endpoint of 0.017 mg/kg/day applies to the general U.S. population and all population subgroups.
3. NA = not applicable. The RfD/Peer Review Committee classified hydramethylnon as a "Group C" (the Reference Dose approach should be used for quantification of human risk).

4.3 Water Exposure/Risk Pathway

In a meeting on 1/22/03, the HED MARC met to discuss the hydramethylnon degradates of concern in drinking water only (see Attachment 1 for structures of all metabolites pertinent to this risk assessment). Environmental fate data suggest that hydramethylnon is relatively persistent and non-mobile in the environment. The major route of dissipation for hydramethylnon appears to be photodegradation.

Laboratory soil metabolism studies indicate that the compound is stable under both aerobic and anaerobic conditions with a half-life of more than a year for each. There is a difference of 1 to 2 orders of magnitude in half-lives between the laboratory soil metabolism study and the terrestrial field dissipation study. The laboratory half-life which is longer than the field half-life was used to estimate drinking and aquatic exposures. Environmental and drinking water concentrations would be lower if the actual half-life of hydramethylnon is closer to that determined from the terrestrial field dissipation study.

Hydramethylnon can be transported to surface water following rainfall events after application. Based on Tier -1 modeling (i.e., FIRST), the acute concentrations are not likely to exceed a peak concentration of **76.09 ppb** which is recommended for estimating acute risks from exposure of humans to hydramethylnon in drinking water from surface water sources. The predicted annual daily average concentration is not likely to exceed **1.45 ppb** which is recommended for estimating chronic risks from exposure of humans to hydramethylnon in drinking water from surface water sources. Hydramethylnon does not appear to substantially leach into soils, based on its high affinity to bind to soil (i.e., K_d = 1039-1725). Based on SCI-GROW modeling, the estimated concentrations in ground water for the proposed pineapple uses are not likely to exceed **0.035 ppb**. This concentration is appropriate for estimating the potential for acute and chronic risks from exposure of humans to hydramethylnon in drinking water from ground water sources.

Table 8. Estimated Tier 1 Concentrations of Hydramethylnon in Drinking Water.

Chemical	Surface Water (ug/L)		Groundwater (ug/L)
	Acute	Chronic	Acute and Chronic
Hydramethylnon	76.09	1.45	0.035

4.4 Residential Exposure/Risk Pathway

Hydramethylnon is labeled for consumer use as a bait in CRP and as a gel bait to control ants and roaches indoors, and as a granular formulation to control ants in yards and on lawns. It is also applied by pest control operators (PCOs) in the same forms for indoor and outdoor pest control. Residents or consumers applying hydramethylnon products to their lawns may be exposed through skin contact or by inhalation. As stated previously, inhalation is not expected to be a significant exposure route due to the low vapor pressure and formulation types of hydramethylnon products. Postapplication dermal exposure for adults and dermal and incidental oral exposures for children contacting treated turf is anticipated. Residential exposure durations are expected to be short-term (less than one month) since ants are expected to carry the bait to their nests. Limited, non-guideline dissipation data are available (see occupational postapplication assessment).

4.4.1 Residential Use Pattern

Ant/roach Bait Stations in CRP for Use Inside Homes

Several bait stations containing less than one percent ai are currently registered for use inside homes for ants and roaches. These products are pre-filled and sold only in child-resistant packaging (CRP). Child-resistant packaging is designed to prevent most children under the age of five from gaining access to the pesticide, or at least delay their access. It does not eliminate the potential for exposure. Since hydramethylnon has relatively low toxicity, is present in bait stations

in less than one percent formulation, and is in child resistant packaging, the risk to children is considered incidental and low. The review of incident and poison control reports indicates no exposure occurs in most cases, and no serious health effects were reported where medical follow up occurred. For a high-end potential exposure scenario, refer to the HED assessment of the incidental ingestion of granular formulation on the lawn.

Granular Formulation Applied to Outdoor Residential Lawns
The current registration request is for a 0.73% ai granular product. In addition, granular/pellet type formulations containing 0.036-0.9 % ai are registered for use on turf and/or gardens to control fire ants and other ants. The product can be applied directly to the area around a mound (2 to 5 tablespoons per mound) or broadcast applied at rates up to 2 lbs of product (0.02 lb ai) per acre, by residents or by professional applicators.

4.4.1.1 Residential Handler Exposure

The following are the major potential handler exposure scenarios for the application of granular formulation to residential sites:

- applying granular formulation with spoon or disposable cup
- loading/applying granular formulation using belly grinder
- loading/applying granular formulation using push-type spreader
- applying gel bait formulation with bare hands and syringe applicator

NOTE: again, it is assumed no exposure results from placing CRP bait stations. Gel application by syringe is assumed to result in negligible exposure, but may be compared to granular application.

The following assumptions were used for handler assessments:

Application Rate
Based on labels provided to HED the maximum application rate was assumed to be 0.02 lb ai/acre (2.0 lb product/acre at 1% ai) when applied by professionals, and 0.0146 lb ai/acre (2 lbs product/acre at 0.73 % ai) for consumer applicators (Reg 73342-1, 7-18-02).

Area Treated
Based on the 12/18/97 draft SOPs for Residential Exposure Assessments, it was assumed that homeowners will treat up 20,000 ft^2 (approximately1/2 acre) for full lawn treatments and 1,000 ft^2 (0.023 acres) for spot treatments. The granular product for home is sold in 5 lb bags that treat 10,000 ft^2.

Unit Exposures
The unit exposures used for bare hands and the belly grinder scenarios are based on the PHED version 1.1. as presented in the 12/18/97 draft SOPs for Residential Exposure Assessments.

Additional information regarding the use of PHED is included in the Appendix of this assessment (i.e. policy for its use, number of replicates, data grade, and data confidence levels).

The homeowner unit exposures are based on the homeowner granular push-type spreader study (ORETF Study No. OMA003 -- A Generic Evaluation of Homeowner Exposure Associated with Granular Turf Pesticide Handling and Application to Residential Lawns, Table 9). Non-occupational handler exposures were calculated for the individuals wearing short sleeves and short pants only (except where noted).

Dermal absorbed doses (mg/kg/day) and inhaled doses (mg/kg/day) for both occupational and non-occupational/residential handlers were calculated with the following equation:

$$\textbf{Dermal absorbed dose (mg/kg/day)} = \frac{\text{Rate (lb ai/A)} \times \text{Dermal UE (mg /lb ai)} \times \text{DA} \times \text{Acres Treated (A/day)}}{\text{BW (kg)}}$$

$$\textbf{Inhalation dose (mg/kg/day)} = \frac{\text{Rate (lb ai/A)} \times \text{Inhalation UE (µg/lb ai)} \times \text{(1.0E-3 mg/µg)} \times \text{Acres Treated (A/day)}}{\text{BW (kg)}}$$

Where:

Rate	=	maximum application rate on product label (lb ai/A)
UE (Unit Exposure)	=	Exposure value derived from August 1998 PHED Surrogate Exposure Table or other ORTEF data (mg or µg per lb ai handled).
DA (dermal absorption factor)	=	Factor to account for dermal absorption when endpoint is selected from an oral study (unitless)
Acres Treated	=	Maximum number of acres treated per day (A/day)
BW	=	body weight (kg)

As shown in Table 9, the short-term dermal MOEs calculated for non-occupational handlers applying granular formulations were well above the target MOE of 100 (range 10,000 to 1.6 x 10^6). Exposure due to application of the gel formulation would probably be less than distribution of granules by hand, as a syringe applicator is used.

Table 9. Short-Term Residential Handler Exposure

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[1]	Inhalation Unit Exposure (ug/lb ai)[2]	Crop[3]	Application Rate[4] (lb ai/A)	Daily Area Treated[5] (A/day)	Dermal Dose (mg/kg/day)[6]	Dermal MOE [7]	Inhalation Dose (mg/kg/day)[8]	Inhalation MOE[9]	Total MOE[10]
Applicator										

Table 9. Short-Term Residential Handler Exposure

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[1]	Inhalation Unit Exposure (ug/lb ai)[2]	Crop[3]	Application Rate[4] (lb ai/A)	Daily Area Treated[5] (A/day)	Dermal Dose (mg/kg/day)[6]	Dermal MOE [7]	Inhalation Dose (mg/kg/day)[8]	Inhalation MOE[9]	Total MOE[10]
Applying Granulars for Hand application (1)	430	470	Lawn broadcast	0.02	0.023	0.000028	60000	0.0000031	550000	54000
Mixer/Loader/App										
Loading/Applying Granulars for Push-type spreader (ORETF) application (2)	0.67	0.88	Lawn broadcast	0.02	0.5	0.00000096	1800000	0.00000013	14000000	1600000
Loading/Applying Granulars for Belly Grinder application (3)	110	62	Lawn broadcast	0.02	0.5	0.00016	11000	0.0000089	190000	10000
Loading/Applying Granulars for Belly Grinder application (4)	110	62	Lawn broadcast	0.02	0.023	0.0000072	240000	0.00000041	4200000	220000

[1]Baseline dermal unit exposures represent long pants, long sleeved shirts, shoes, and socks. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[3]Crops and use patterns are based on labels and BEAD data.
[4]Application rates are based on maximum values found on various labels. In most scenarios, a range of maximum application rates is used to represent the range of rates for different crops/sites/uses. Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon). Some labels specify tablespoons/fire ant mound, but the higher broadcast rate was used for range finding risk estimate.
[5]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[6]Dermal dose (mg/kg/day) = [unit exposure (mg/lb ai) * Dermal absorption (1%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[7]Dermal MOE = Oral NOAEL (1.7 mg/kg/day) / Daily Dermal Dose. Target Dermal MOE is 100.
[8]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[9]Inhalation MOE = Oral NOAEL (1.7 mg/kg/day) / Daily Inhalation Dose. Target Inhalation MOE is 100.
[10] Total MOE = Oral NOAEL (1.7 mg/kg/day)/ Total (Dermal + Inhalation) Dose

4.4.1.2 Postapplication

The following are the major exposure scenarios following the application of granular formulation to residential sites:

- dermal exposure via contact with treated turf-grass
- oral hand-to-mouth exposure via contact with treated turf-grass
- oral ingestion of granules

Screening-level assessments for these 3 scenarios were completed and are based on the draft 12/18/97 Standard Operating Procedures (SOPs) for Residential Exposure Assessments (revised with additional peer-reviewed data 02/01).

Dermal Exposure via Contact with Turf-grass
The following equations were used to calculate dermal exposures from contact with treated turf-grass:

$$\mathbf{DFR_t}\ (ug/cm^2) = \text{Application Rate (lb ai/acre)} \times F \times (1\text{-}D)^t \times 4.54E8\ \mu g/lb \times 24.7E\text{-}9\ acre/cm^2$$

where:
DFR_t = dislodgeable foliar residue on day "t" (ug/cm^2)
Rate = application rate (lb ai/acre)
F = fraction of ai retained on foliage (unitless)
D = fraction of residue that dissipates daily (unitless)

Adult and children's dermal daily dose following the application of hydramethylnon on lawns was calculated using the following equation:

$$\textbf{Dermal Absorbed Dose} = \frac{DFR_t\ (ug/cm^2) \times DA \times 0.001\ mg/ug \times Tc\ (cm^2/hr) \times ET\ (hrs)}{\text{Body Weight (kg)}}$$

where,
DFRt = dislodgeable foliar residue on day "t" (ug/cm^2)
DA = dermal absorption factor (unitless)
Tc = transfer coefficient (cm^2/hr)
ET = exposure time (hrs)

The Dermal MOE was calculated as follows:

Dermal MOE = NOAEL (mg/kg/day) / Dermal Dose (mg/kg/day)

The following assumptions were used to calculated dermal exposures and MOEs:

- The body weights of adults and children are assumed to be 70kg and 15 kg, respectively.

The activities that were selected as the basis for the risk assessment are represented by the following transfer coefficients (for short-term endpoints):

- **Transfer Coefficient = 14,500 cm^2/hour** for adults involved in a high exposure activity on turf such as heavy yard work or laying sod; and
- **Transfer Coefficient = 5,200 cm^2/hour** for children (1-6 year olds) involved in a high exposure activity. Based on the proposed changes to the Residential SOPs, transfer coefficients of 14,500 cm^2/hr for adults and 5,200 cm^2/hour for small

children were used to calculate dermal exposures to treated turf.

As shown in Table 10, the dermal MOEs calculated for a 70 kg adult and 15 kg child were well above the target MOE of 100 (MOE = 24,000 for child; MOE = 41,000 for adult). Also, the product is a bait and is often applied directly to ant hills and is carried off by the ants. Therefore, even less exposure is anticipated than represented by the quantitative assessment.

Table 10. Post-application Dermal Exposure and Risk From Playing/Working on Treated Turf-grass Immediately after Treatment with Hydramethylnon

Scenario	Rate (lb ai/ acre)	Day '0' DFR [1] (ug/cm^2)	Tc (cm^2/hr)	Dermal Absorbed Dose [2] (mg/kg/day)	MOE
			Short-term	Short-term	Short-term
Adults (70 kg)	0.02	0.01	14500	0.000042	41000
Children (15 kg)	0.02	0.01	5200	0.00007	24000

[1] Day '0' DFR (ug/cm^2) = Rate (ai/acre) x 0.05 x 4.54E8 µg/lb x 24.7E-9 acre/cm^2

[2] Daily Dose = $\frac{\text{(DFR x Absorption Factor (0.01) x 0.001 mg/ug x Tc (cm}^2\text{/hr) x Exposure Time (2 hrs)}}{\text{Body Weight (kg)}}$

[3] Dermal MOE = $\frac{\text{NOAEL (1.7 mg/kg/day)}}{\text{Dermal Absorbed Dose (mg/kg/day)}}$

Incidental Ingestion from Turf-grass

The Agency's Residential SOPs contains guidance for considering children's exposure to treated turf. The dermal calculations, as noted above, were completed based on the guidance provided in the document. All nondietary ingestion exposures were also calculated using guidance from this document. Specifically, the kinds of nondietary exposures that were considered in this assessment include the following:

- **Dose from eating granules calculated using Residential SOP 2.3.1:** Postapplication potential dose among children from incidental, episodic nondietary ingestion of pesticide granules in the treated area.
- **Dose from hand to mouth activity calculated using Residential SOP 2.3.2:** Postapplication potential dose among small children from incidental nondietary ingestion of pesticide residues on residential lawns from hand-to-mouth transfer.
- **Dose from mouthing treated turf or contaminated objects calculated using Residential SOP 2.3.3:** Postapplication potential dose among children from the ingestion of pesticide treated turfgrass; and
- **Dose from incidental ingestion of soil calculated using Residential SOP 2.3.4:** Postapplication potential dose among children from the ingestion of soil in pesticide treated

areas.

Although incidental exposures incurred by hand-to-mouth exposure are included as part of the nondietary risk assessment, granular ingestion is considered *episodic* in nature. Therefore, the granular ingestion is assessed as an individual event and is not combined with any other nondietary exposure. The hand-to-mouth, object mouthing, and eating of soil are considered more likely to co-occur, and thus are combined. Note that the hand-to-mouth scenario constitutes the largest incidental oral exposure component (see Table 11).

The assumptions and formulae used to estimate nondietary exposure are detailed in Attachment 2.

Children's oral exposure from hand-to-mouth ingestion from contact with treated turf-grass was calculated with following equation:

$$\textbf{Oral Dose}_{t} = \frac{DFR_{t}\ (ug/cm^2) \times SA\ (cm^2/event) \times SEF \times FQ\ (events/hr) \times 1.0E\text{-}3\ mg/ug \times ET\ (hrs/day)}{\text{Body Weight (kg)}}$$

where,

DFRt = dislodgeable foliar residue on day "t" (ug/cm^2)
SA = surface area of hands that inserted in child's mouth (cm^2/event)
SEF = saliva extraction factor (unitless)
FQ = frequency of hand-to-mouth activity (events/hour)
ET = exposure time (hrs)

The Dermal MOE was calculated as follows:

Dermal MOE = NOAEL (mg/kg/day) / Dermal Dose (mg/kg/day)

The following assumptions were used to calculate **children's oral hand-to-mouth exposure** from treated turf:

- The fraction of ai that is available for hand-to-mouth contact on day '0' is assumed to be 0.05 (5% of maximum application rate).
- The maximum application rate of 0.02 lb ai/acre was assumed.
- The surface area (SA) of hands inserted in child's mouth is assumed to be 20 cm^2/event (based on the palmer surface area of a child's 3 fingers being 20 cm^2).
- The saliva extraction factor (SEF) was assumed to be 0.5 (50%).
- The frequency (FQ) of hand-to-mouth activity was assumed to be 20 events/hour.
- The exposure time (ET) is 2 hours
- A body weight of 15 kg was assumed for children.
- The oral daily dose calculated for the post-application assessment was assumed to be a central to high-end value.

As shown in Table 11, the calculated short-term MOEs were well above the target MOE of 100

(range 5,200 to 150,000) with an aggregate of all hand-mouth oral exposures resulting in a MOE of 4,000. The incidental ingestion of granules directly from the treated area resulted in a MOE of 850.

Table 11. Residential Short-term Oral Nondietary Postapplication Risks to Children (1-6) from "Hand-to-Mouth" and Ingestion Exposure When Reentering Lawns Treated with Granular Hydramethylnon Formulations

Type of Exposure	Application Rate[a] (lb ai/acre)	Ingestion Rate or Other Assumptions[b]	Oral Dose[c] (mg/kg/day)	MOE[d]
Hand to Mouth Activity	0.022	Residential SOPs	0.00033	5200
Turfgrass/Object Mouthing	0.022	Residential SOPs	0.000082	21000
Ingestion of Soil	0.022	Residential SOPs	0.000011	150000
Total of the Oral Exposures Above[e]	Granular formulation		0.00042	4000
Incidental Ingestion of Granules	1% ai	3 mg/day	0.002	850

Footnotes:

a Application rates represent maximum label rates from current EPA registered labels.
b Assumptions from Draft Residential SOP's (1997, revised 2/01).
c Oral doses calculated using formulas presented in the Residential SOPs (December, 1999). Short-term doses were calculated using the following formulas.

Hand-to-mouth; in the absence of DFR data, Revised Residential SOPs (02/01) are used: oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [application rate (lb ai/acre) x fraction of residue dislodgeable with potentially wet hands (5%) x 11.2 (conversion factor to convert lb ai/acre to $\mu g/cm^2$)] x median surface area for 1-3 fingers (20 cm^2/event) x hand-to-mouth rate (ST: 20 events/hour) x 50% saliva extraction factor x exp. time (2 hr/day) x 0.001 mg/µg] / bw (15 kg child).

Grass/object mouthing; oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [application rate (lb ai/acre x 11.2 (conversion factor to convert lb ai/acre to $\mu g/cm^2$)) x fraction of residue dislodgeable (20%) x ingestion rate of grass (25 cm^2/day) x .001 mg/µg] / bw (15 kg child).

Soil ingestion; oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [(application rate (lb ai/acre) x fraction of residue retained on uppermost 1 cm of soil (100% or 1.0/cm) x 4.54E+08 µg/lb conversion factor x 2.47E-08 acre/cm^2 conversion factor x 0.67 cm^3/g soil conversion factor) x 100 mg/day ingestion rate x 1.0E-06 g/µg conversion factor] / bw (15 kg). Short term dose based residue on the soil on day of application.

Granular pellet ingestion: (mg/kg/day) oral dose to child (1-6 year old) = [Granule ingestion rate adjusted for application rate (3 mg/day) x Fraction of ai of granule formulations (1%)] / bw (15 kg).

d Oral MOE = Oral NOAEL (1.7 mg/kg/day for short-term assessments) / Oral Dose (mg/kg/day). Oral NOAEL determined from a rat study. MOEs are reported to two significant figures; target MOE is at least 100.
e Combined MOE may be obtained by dividing oral NOAEL by sum of oral doses, or by taking the inverse of the sum of the inverses of the MOEs: Combined MOE = 1/[$1/MOE_1 + 1/MOE_2$ etc.]

4.4.1.3 Combined Residential Exposure

FQPA requires that all exposures that could reasonably be expected to occur on the same day be combined and compared to the appropriate toxicity endpoint. The residential scenarios that can reasonably be expected to occur on the same day for toddlers/children are listed in Table 12.

Table 12. Exposure Potential for Adult and Child Short-term Aggregate Risk Estimates for Hydramethylnon.

Exposure Scenario		Exposure (Dose) mg a.i./kg bw/day	MOE	Combined Exposure (Dose) mg a.i./kg bw/day	COMBINED MOE[1]
Toddler - Treated Turf	Total Oral nondietary post-application exposure from contacting treated turf	0.00042	4000	0.00049	3500
	Dermal post-application exposure from contacting turf	0.00007	24000		
Adult - Treated Turf	Handler dermal and inhalation exposure from applying hydramethylnon using belly grinder spreader	0.00017	10000	0.00021	8000
	Dermal post-application exposure from contacting treated turf	0.000042	41000		

[1] Combined MOEs are presented for toddler oral + dermal exposure to treated turf. Combined MOEs are expressed as: $MOE_{DERMAL} + MOE_{ORAL}$. Combined MOEs are presented for an adult who applies the material to his/her lawn and then experiences post-application exposure. MOEs combined from different sources of exposure (i.e., application + post-application) are expressed as: $MOE_{applicator} + MOE_{post\text{-}application}$.

2. HED believes handler exposure will be negligible. However, the results from an unpublished study (see residential post-application exposure to treated pets) were use to measure possible post-application exposure. HED herein used the data from sampling at ten minutes post-application and assumes that a pesticide handler would not receive a greater dose if applied according to label directions than what was measured via cotton glove dosimetry from purposeful stroking of treatment loci (see Section 4.4.1.1 Residential Handler of this risk assessment).

4.4.1.4 Bait Stations in Child Resistant Packages (CRP)

Although for CRPs "... nearly all exposures involve, at most, children mouthing the bait container with little or no contact with the actual bait" (DP Barcode: D231127, Rereg. Case: 2585, J. Blondell, 8/27/97), and the bait station should be normally considered an article and accidental exposure to the internal contents of bait stations would not be expected, HED acknowledges that the CRP is not child proof. Several bait stations containing 0.01% to 1% ai are currently registered for use inside homes for ants and roaches. These products are pre-filled and designed to prevent most children under the age of five from gaining access to the pesticide, or at least delay their access. It does not eliminate the potential for exposure. If a child were to open and ingest the contents of an entire bait station , there is no acute dietary endpoint for children which could be used to calculate an acute risk. However, using the subchronic endpoint dose of 1.7 mg/kg/day, a child consuming a bait trap containing 21 mg of active ingredient by a child would result in a MOE slightly greater than 1. In order to attain an MOE of 100, no more than 4 mg ai should be ingested

by a 15 kg child (19% of one bait station). This result is similar to determinations for other active ingredients (Human Health Risk Assessment for Sulfluramid, DP Barcode: D266052, S. Weiss, 3/27/01).

4.4.2 Non-occupational Off-Target Exposure

Unintentional exposure due to drift during ground or aerial application is unlikely because hydramethylnon is formulated only as a granular for broadcast application.

4.5 Incidents

A review of the HED Incident Data System conducted in March 2003 shows that hydramethylnon products continue to be the subject of many incident reports. Nearly all (96%) the children under six years of age exposed to hydramethylnon products (280 reports to Poison Control Centers with follow-up per year, 1993-98) did not experience any symptoms and a small proportion exhibited mostly minor effects which did not require medical attention. The number of incidents reported appear to be a function of the sheer volume of bait stations and widespread use of other hydramethylnon products, with no increase in rate of serious symptoms. Of course, incidents should continue to be monitored.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for the following scenarios: acute aggregate exposure (food + drinking water), short-term aggregate exposure (food + drinking water + residential), and chronic aggregate exposure (food + drinking water). Since the short-and intermediate-term endpoints are the same, an intermediate- term aggregate risk assessment was not performed because the short-term exposure assessment would be the worst-case to assess both exposure durations. A separate cancer aggregate risk assessment was not performed because the Reference Dose approach was recommended for quantification of human risk. All potential exposure pathways were assessed in the aggregate risk assessment. Dietary (food and drinking water), handler and post-application residential exposures were considered, as necessary, because there is a potential for individuals to be exposed concurrently through these routes.

Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxicity endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate DWLOCs, the dietary food estimates (from DEEM-FCID™) were subtracted from the

PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (US Population, adult male, and youth), 60 kg/2L (adult female), and 10kg/1L (infants and children).

For acute and chronic dietary exposure, HED is concerned when estimated dietary risk exceeds 100% of the aPAD and cPAD, respectively. HED's level of concern for residential oral, dermal and inhalation exposures are for MOEs <100. For hydramethylnon, short-term oral, dermal and inhalation exposures estimates can be aggregated due to the common toxicity endpoint (testicular effects).

5.1 Acute Aggregate Risk Assessment (Food and Drinking Water)

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of hydramethylnon (food and drinking water). The dermal, inhalation, and incidental oral exposures resulting from short-term residential applications are assessed separately.

A Tier 1 (conservative, deterministic assessment using tolerance-level residues, 100% crop treated (CT) for the proposed commodity; and DEEM-FCID™; ver. 1.30, processing factors set to 1) acute dietary exposure assessment was conducted for the female 13-50 yrs old population subgroup. The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for the female 13-50 population subgroup (<1% of the aPAD). The EECs generated by EFED are less than HED's calculated DWLOCs for acute exposure to hydramethylnon in drinking water. Therefore, the acute aggregate risk associated with the proposed use of hydramethylnon does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 13 summarizes the acute aggregate exposure estimates to hydramethylnon residues.

Table 13. Acute Aggregate Exposures to Hydramethylnon Residues.

Population Subgroup	aPAD (mg/kg/day)	Acute Food Exposure (mg/kg/day)	Maximum Acute Water Exposure [1] (mg/kg/day)	Ground Water EEC [2] (µg/L)	Surface Water EEC [2] (µg/L)	Acute DWLOC [3] (µg/L)
Females (13-49 years old)	0.05	0.000004	0.049996	0.035	76.09	1500

[1] maximum water exposure (mg/kg/day) = aPAD (mg/kg/day) - food exposure (mg/kg/day)

[2]The crop producing the highest level was used.

[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

5.2 Short-term Aggregate Risk Assessment

The short-term aggregate risk assessment estimates risks likely to result from 1- to 30-day exposure to hydramethylnon residues from food, drinking water, and residential pesticide uses. High-end

estimates of the residential exposure are used in the short-term assessment, and average values are used for food and drinking water exposures.

Short-term aggregate risk assessments are required for adults as there is potential for both dermal and inhalation handler exposure, and dermal post-application exposure from the residential uses of hydramethylnon on turf. In addition, short-term aggregate risk assessments are required for children/toddlers because there is a potential for oral and dermal, post-application exposure resulting from the residential uses of hydramethylnon on turf. The short-term residential exposure potential from the turf uses for adults and children/toddlers can be found in Table 12. The turf-treatment resulted in exposures for both adults (MOE = 8,000; handler and post-application) and children (MOE = 680; post-application). Therefore, the turf-treatment exposure estimates were aggregated with the chronic dietary (food) to provide a worst-case estimate of short-term aggregate risk for the U.S. population and children 1-2 years old (the child population subgroup with the highest estimated average (chronic) dietary food exposure) (see Table 7).

Table 14. Short-Term Aggregate Risk and DWLOC Calculations for Hydramethylnon.

Population Subgroups	Short-Term Scenario									
	NOAEL (mg/kg/day)	Level of Concern[1]	Max Exposure[2] (mg/kg/day)	Average Food Exposure (mg/kg/day)	Residential Exposure [3] (mg/kg/day)	Aggregate MOE (food and residential)[4]	Max Water Exposure[5] (mg/kg/day)	Ground Water EEC[6] (ug/L)	Surface Water EEC[6] (ug/L)	Short-Term DWLOC[7] (µg/L)
US Population	1.66	100	0.017	0.000005	0.00021	7700	0.016785	0.035	1.45	580
Children 1-2 years old	1.66	100	0.017	0.000026	0.00049	3300	0.016484	0.035	1.45	165

[1] The level of concern (target MOE) includes 10X for interspecies extrapolation and 10X for intraspecies variation.
[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE
[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. See Table 12.
[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]
[5] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)
[6] The crop producing the highest level was used.
[7] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{\left(\text{maximium water exposure (mg / kg / day)}\right) * \left(\text{body weight (kg)}\right) * \left(1000\ \mu\text{g / mg}\right)}{\text{water consumption (liter / day)}}$$

As the MOEs are greater than 100, the short-term aggregate risks are below HED's level of concern. For surface and ground water, the estimated average concentrations of hydramethylnon are less than HED's calculated DWLOCs for hydramethylnon in drinking water as a contribution to short-term aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of hydramethylnon in drinking water do not contribute significantly to the short-term aggregate human health risk at the present time.

5.3 Chronic Aggregate Risk Assessment (Food and Drinking Water)

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of hydramethylnon (food and drinking water) and residential uses. However, due to the use patterns, no chronic residential exposures are expected. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only.

The Tier 1 (conservative, deterministic assessment using tolerance-level residues, 100% crop treated (CT) for the proposed commodity; and DEEM-FCID™; ver. 1.30, processing factors set to 1) chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (<1% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at <1% (0.02%) of the cPAD. The Tier 1 EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to hydramethylnon in drinking water. Therefore, the chronic aggregate risk associated with the proposed use of hydramethylnon does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 15 summarizes the chronic aggregate exposure estimates to hydramethylnon residues.

Table 15. Chronic Aggregate Exposures to Hydramethylnon Residues.

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure[1] (mg/kg/day)	Ground Water EEC[2] (µg/L)	Surface Water EEC (µg/L)	Chronic DWLOC[3] (µg/L)
U.S. Population	0.017	0.000005	0.016995	0.035	1.45	600
All infants (< 1 year old)	0.017	0.000012	0.016988	0.035	1.45	170
Children (1-2 years old)	0.017	0.000026	0.016974	0.035	1.45	170
Children (3-5 years old)	0.017	0.000016	0.016984	0.035	1.45	170
Children (6-12 years old)	0.017	0.000008	0.016992	0.035	1.45	170
Youth (13-19 years old)	0.017	0.000002	0.016998	0.035	1.45	170
Adults (20-49 years old)	0.017	0.000003	0.016997	0.035	1.45	600
Females (13-49 years old)	0.017	0.000004	0.016996	0.035	1.45	510
Adults (50+ years old)	0.017	0.000002	0.016998	0.035	1.45	600

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)
[2] NR = not recorded.
[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether hydramethylnon has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to hydramethylnon and any other substances and hydramethylnon does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that hydrametylnon has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE

Registered Use Sites

Hydramethylnon is currently registered for use on nursery trees and plants, ornamental plants, pastures, forage, rangeland, roadsides, rights-of-way, forests, Christmas tree farms, lawns, and golf courses. Other non-agricultural uses include: farm animals; commercial, industrial, and residential buildings; recreational areas; all types of vehicles; food processing areas; meat and poultry plants; garbage dumps and waste sites; and caskets.

7.1.1 Application Rates and Timing and Frequency of Application

Hydramethylnon may be applied up to six times per season for pineapple and other agricultural uses, depending on the label. Application rates for broadcast granular formulation range from 0.007 lb ai/A to 0.022 lb ai/A, although rates are indeterminate when individual mounds are treated at the rate of 5 tablespoons per mound. Some labels specify indoor treatments. See Table 16 for more detailed label information.

Table 16. Current and Proposed End-use Products Containing Hydramethylnon

Product Name / REG	Formulation /	App. rate	Max. No.	Use Pattern	Comments

No.	% ai		App./Yr		
[PROPOSED LABEL] AMDRO Fire Ant Insecticide/Granular Insecticide/Pro Fire Ant Bait / SIEGE Pro Fire Ant Bait 241-322	Granular 0.73	0.0073-0.022 lb ai/A	6 (at 0.0073 lb ai/A)	Pineapple	Aerial / Ground Broadcast by Disc or Turbine Blower

7.1.2 Methods and Types of Equipment used for Mixing, Loading, and Application

Hydramethylnon in granular bait formulation may be applied to pineapple fields and directly on ant mounds using hand held equipment (spoon, scoop, etc.), ground equipment (tractor drawn disc spreader or turbine blower type), or by aerial application. Use and equipment information was provided by the Pineapple Growers Association of Hawaii (April, 2003, electronic communication) based on use of hydramethylnon under emergency use and Section 18 permits. Most growers reported using helicopters lifting hoppers with spinning disk spreaders for large fields, with tractor-pulled turbine blowers used for smaller areas and near roads, although some growers only applied by ground equipment.

7.2 Occupational Handler Exposures & Risks

The Agency has determined that there are potential exposures to loaders, applicators, and other handlers during usual use-patterns associated with hydramethylnon. Based on the use patterns, 6 major exposure scenarios were identified for hydramethylnon which could be assessed quantitatively:

- Loading granular product for aerial application
- Loading granular product for mechanized ground spreader application
- Applying granular products by helicopter*
- Flagging aerial application of granular product
- Applying granular products by tractor-drawn spreader
- Applying granular products by blower-spreader**

* data are only available for closed cockpit fixed wing aircraft; these are considered a surrogate for helicopter application

**no data are available for these scenarios; surrogate granular spreader PHED data were used (see text)

Handler Exposure Scenarios -- Data and Assumptions

Occupational handler exposure assessments are evaluated by the Agency using a baseline clothing exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve a margin of exposure (MOE) which does not exceed the Agency's level of concern for hydramethylnon (see Table 17). Current labeling for broadcast spreading of granules calls for wearing

chemical resistant gloves.

No chemical-specific exposure data were submitted for the registration of hydramethylnon. In the absence of chemical-specific data, it is the policy of HED to utilize the unit exposure values from the Pesticide Handler Exposure Database (PHED) V 1.1. As stated previously, this chemical has a low vapor pressure and is formulated with an oil, therefore inhalation exposure is expected to be no greater than other pesticides in the HED's database of pesticide exposure. The Agency uses PHED as a primary source of surrogate exposure data because the data contained in the system have undergone an extensive quality control/quality assurance review process as has the system itself (i.e., values calculated using PHED can be considered reliable based on the data included in the system). [See Attachment 2 for a more complete description of the PHED]. All of the handler exposure scenarios were estimated using PHED.

There are no available surrogate or chemical-specific data which are considered representative of the "buffalo blower" or air-assisted granular spreader. The Biological and Economic Analysis Division (BEAD) estimated that up to ten 25 lb bags of granular product could be loaded and applied using one of these air-assisted blowers, traveling at 2.5 miles per hour. Therefore, the total amount was used in combination with the available PHED data for granular spreader loader/applicator exposures to estimate daily exposure. Usually, 40 acres is used in assessing the daily exposure when using granular spreaders; this was adjusted to 125 acres at 2 lbs of 1% product per acre to be equivalent to 250 lbs product handled per day. Previously, BEAD has estimated between 10,000 and 36,000 acres of Hawaiian pineapple may be treated annually for fire ants using hydramethylnon.

7.2.1 Handler Exposure and Risk Estimate Methodology

Durations of exposure are anticipated to be short-term (1-30 days) and intermediate-term (one to several months) for occupational assessments. Based on the labeled use pattern, most agricultural workers are expected to handle hydramethylnon (load or apply) less than 30 days per year, although some may handle the products more than 30 days, but probably less than six months per year. In this case, it is not necessary to calculate the intermediate-term exposure since, using the same dose to estimate risk, the short-term estimates represent the most conservative MOEs.

Handler exposure assessments are conducted using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate margin of exposure. The baseline scenario generally represents a handler wearing long pants, a long-sleeved shirt, and no chemical-resistant gloves. Chemical-resistant gloves are required on the agricultural-use labels. There were no data for hand dispersal of granules without gloves, so only the gloved scenario is presented. Also aerial application data were only available for fixed-wing plane pilots in enclosed cockpits.

Potential daily exposures were calculated using the following formulae:

$$\textit{Daily Dermal Exposure}\left(\frac{mg\ ai}{day}\right) = \textit{Unit Exposure}\left(\frac{mg\ ai}{lb\ ai}\right) \times \textit{Use Rate}\left(\frac{lb\ ai}{A}\right) \times \textit{Daily Acres Treated}\left(\frac{A}{day}\right)$$

$$Daily\ Inhalation\ Exposure\left(\frac{mg\ ai}{day}\right) =$$
$$Unit\ Exposure\left(\frac{\mu g\ ai}{lb\ ai}\right) x\ Conversion\ Factor\left(\frac{1mg}{1{,}000\ \mu g}\right) x\ Use\ Rate\left(\frac{lb\ ai}{A}\right) x\ Daily\ Acres\ Treated\left(\frac{A}{day}\right)$$

Inhalation and dermal doses were calculated using the following formulae:
where: inhalation absorption factor is assumed to be 100 percent for both short- and intermediate

$$Daily\ Inhalation\ Dose\left(\frac{mg\ ai}{kg/day}\right) = Daily\ Inhalation\ Exposure\left(\frac{mg\ ai}{day}\right) x\left(\frac{Inhalation\ AbsorptionFactor(\frac{percent}{100})}{body\ weight\ (kg)}\right)$$

term doses.

$$Daily\ Dermal\ Dose\left(\frac{mg\ ai}{kg/day}\right) = Daily\ Dermal\ Exposure\left(\frac{mg\ ai}{day}\right) x\left(\frac{Dermal\ Absorption\ Factor\ (\frac{percent}{100})}{body\ weight\ (kg)}\right)$$

where: dermal absorption is assumed to be 1 percent or 0.01 for the short- and intermediate-term assessments.

7.2.2 Summary of Exposure and Risk Estimates: Concerns for Handlers, Data Gaps, and Confidence Levels

Short/Intermediate-term Exposure Duration Risk Estimates

The short- and intermediate-term handler exposure and risk estimates are shown in Table 17. This table shows baseline handlers' exposure, where data were available: hand dispersal data are only available with chemical-resistant gloves, and the engineering control (closed cockpit) only data were available for aerial applicators. The PHED-based exposure and risk estimates for occupational handlers were all below the level of concern (i.e., all MOEs > 100). The MOEs ranged from 9500 at baseline for loading granulars for aerial application to 220,000 for hand dispersal of granular formulations.

Table 17. Hydramethylnon Handler Exposure and Risk

Exposure Scenario (Scenario #)	Dermal Unit Exposure (mg/lb ai)[1]	Inhalation Unit Exposure (ug/lb ai)[2]	Crop[3]	App. Rate[4] (lb ai/A)	Daily Area Treated[5] (A/Day)	Dermal Dose (mg/kg/day)[6]	Dermal MOE[7]	Inhalation Dose (mg/kg/day)[8]	Inhalation MOE[9]	Total MOE[10]
Mixer/Loader (Baseline)										
Loading Granulars for Aerial application (1)	0.0084	1.7	Pineapple	0.02	350	0.0000084	200000	0.00017	10000	9500
Loading Granulars for Tractor-Drawn Spreader / Blower (2)	0.0084	1.7	Pineapple	0.02	125	0.000003	570,000	0.000061	28,000	27,000
Applicator (Baseline Clothing)										
Applying Granulars by Tractor-Drawn Spreader /Blower (3)	0.0099	1.2	Pineapple	0.02	125	0.0000035	480,000	0.000043	40,000	37,000
Applicator (Gloves)										
Applying Granulars by Hand (4)	71	470	Pineapple	0.02	0.023	0.0000047	360000	0.0000031	550000	220000
Applicator (Engineering Controls)										
Applying Granulars by Closed Cockpit Airplane (5)	0.0016	1.3	Pineapple	0.02	350	0.0000016	1100000	0.00013	13000	13000
Flagger										
Flagging for Granular aerial application (6)	0.0028	0.15	Range / Pasture / Pineapple	0.02	350	0.0000028	610000	0.000015	110000	96000

[1]Baseline dermal unit exposures represent long pants, long sleeved shirts, shoes, and socks. Gloved data only for granular hand broadcast. Closed cockpit only data for aerial applicator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.
[2]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998.
[3]Crops and use patterns are from labels and BEAD Data.
[4]Application rates are based on maximum values found on proposed label. Specific application rates for 'buffalo blower' based on max 250 lbs handled/day per BEAD data.
[5]Amount treated is based on the area that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[6]Dermal dose (mg/kg/day) = [unit exposure (mg/lb ai) * Dermal absorption (1%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[7]Dermal MOE = NOAEL (1.7 mg/kg/day) / Daily Dermal Dose. Target Dermal MOE is 100.
[8]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[9]Inhalation MOE = NOAEL (1.7 mg/kg/day) / Daily Inhalation Dose. Target Inhalation MOE is 100.
[10]Total MOE = NOAEL/Total Exposure

7.2.3 Data Gaps

There are no exposure data for application of granular formulation using the granular bait blower. Although the risk estimates were not of concern, there is uncertainty as to how similar the PHED surrogate unit exposure data were to the blower equipment.

7.2.4 Data Quality and Confidence in Assessment

Data Quality and Confidence in Assessment

Several issues must be considered when interpreting the occupational exposure risk assessment. These include:

- The aerial applicator assessment was completed using "low quality" PHED data due to the lack of a more acceptable data set.
- Because of the scaling up of the granular broadcast scenario exposure data to fit the air assisted granular blower, there is increased uncertainty in the outcome, but also increased conservatism.
- Risk estimates assume consecutive or frequent daily exposure for up to one month and compare the dose to a multi-generational study endpoint, whereas the unacceptable dermal study had no endpoint at the highest dose tested. Therefore, the risk for someone exposed intermittently would be less than for someone exposed on a daily basis.

7.3 Postapplication Exposures and Risk Estimates

7.3.1 Postapplication Exposure Scenarios

Hydramethylnon currently has an agricultural worker restricted entry interval (REI) of 12 hours postapplication, during which time entry into the treated area is prohibited except with specified personal protective equipment (PPE) unless there is no contact with treated surfaces. Several sources support a rapid dissipation of hydramethylnon in daylight, with a half-life of 12 to 18 hours, and further depletion by the foraging of the target insects (source: R.K. Van Meer, et al., 1982, and registrant documentation,1982). The active ingredient is fairly stable in the dark (up to 2.8 months).

The Agency has determined that there are potential postapplication exposures to individuals re-entering hydramethylnon treated areas for the purpose of: agricultural practices, such as scouting, irrigation, pruning, or harvesting. However, the short half-life of hydramethylnon in daylight should be considered when interpreting the postapplication exposure estimates (see Attachment 2: Occupational Postapplication Exposure and Risk Estimate Tables).

Because hydramethylnon has a low vapor pressure (2.7×10^{-6} PA or 2.0×10^{-8} mm Hg) and is prepared in an oil-based granular bait formulation, the inhalation component of postapplication exposure is anticipated to be negligible. Therefore, all calculations of postapplication risk estimates have been done for dermal exposure only, and there was no need to combine postapplication exposure routes for workers.

7.3.2 Exposure and Risk Calculations

Short- and intermediate-term daily absorbed doses and MOEs were calculated as follows:

$$Dose\ (mg/kg/d) = \frac{(DFR\ (\mu g/cm^2)\ x\ Tc\ (cm^2/hr)\ x\ CF\left(\frac{1\ mg}{1{,}000\ \mu g}\right)\ x\ Abs\ x\ ED\ (hrs/day))}{BW}$$

Where:

DFR	=	daily DFR, as calculated above for the assumed average reentry day
Tc	=	transfer coefficient;
CF	=	conversion factor (i.e., 1 mg/1,000 µg)
Abs	=	dermal absorption (1 percent for short- and intermediate-term)
ED	=	exposure duration; 8 hours worked per day
BW	=	body weight (70 kg for short-term and 60 kg for intermediate-term)

Dermal MOEs were calculated as follows:

$$MOE = \frac{NOAEL\ (mg/kg/day)}{Dose\ (mg/kg/day)}$$

Where:

NOAEL	=	1.7 mg/kg/day for short-term and intermediate-term
Dose	=	calculated absorbed dermal dose

7.3.3 Postapplication Exposure Risk Estimates

None of the postapplication worker exposure scenarios resulted in risks of concern (see Tables 18 & 18, Attachment 2). Assuming the maximum label rate application, there were no reentry worker risk estimates of concern even at reentry day zero (0), or day of after application. Pineapple workers' exposure estimates resulted in MOEs of 30,000-100,000; these risk estimates were based on bare hand study data, but pineapple workers typically wear gloves to prevent injury from the plant leaves. None of the postapplication worker exposure scenarios resulted in risks of concern.

7.4 Summary of Postapplication Risk Concerns, Data Gaps, and Confidence in Exposure and Risk Estimates

Reentry workers will likely be exposed to very little hydramethylnon, if the bait functions to attract the target pests and the pests take the bait to their nest as intended. Hydramethylnon also degrades rapidly in sunlight, as mentioned previously. Estimated risks were calculated using conservative assumptions regarding available residues and assuming workers do not wear gloves. Therefore, pineapple workers wearing gloves would likely have lower than estimated exposure. Risk estimates

also assume consecutive or frequent daily exposure for up to one month and compare the dose to a multi-generational study endpoint, whereas the unacceptable dermal study had no endpoint at the highest dose tested. Therefore, Risk estimates assume consecutive or frequent daily exposure for up to one month and compare the dose to a multi-generational study endpoint, whereas the unacceptable dermal study had no endpoint at the highest dose tested. Therefore, the risk for someone exposed intermittently would be less than for someone exposed on a daily basis.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

The Agency has recommended that the grass forage tolerance be increased to 2.0 ppm and the grass hay tolerance be increased to 0.1 ppm (Hydramethylnon RED, EPA 738-R-98-023, 12/98).

8.2 Toxicology

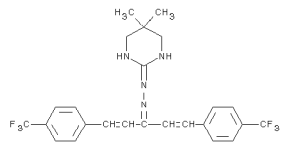
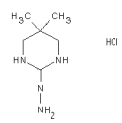
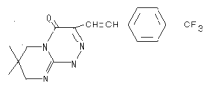
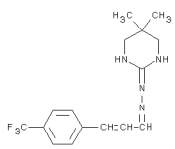
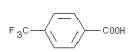
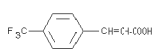
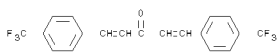
Although a 28-day inhalation study is not available for hydramethylnon, HED has concluded it is not needed for the proposed use on pineapples (G. Bangs, 5/21/03, D290315, TXR# 0051961).

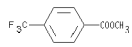
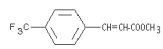
9.0 ATTACHMENTS

Attachments:
1. Summary of Metabolites Discussed in Risk Assessment.
2. Standard Assumptions and PHED Surrogate Tables for Occupational and Non-Occupational Assessments

cc: RAB 2 RF

Attachment 1: Summary of Metabolites Discussed in Risk Assessment.

Identification of Hydramethylnon and Metabolites		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
CL 217300	hydramethylnon	
CL 85646	2-hydrazino-1,4,5,6,-tetrahydro-5,5-dimethyl-pyrimidine	
CL 247176	1,6,7,8-tetrahydro-7,7-dimethyl-3-[p-(trifluromethyl) -styryl-4H-pyrimido[2,1-c]as-triazo-4-one	
CL 252021	cinnamaldehyde, p-(trifluromethyl)-, (1,4,5,6-tetrahydro-5,5-dimethyl-2-pyrimidinyl)hydrazone	
CL 71640	p-toluic acid, a,a,a, -trifluro	
CL 243236	cinnamic acid, p-trifluromethyl-	
CL 98724	1,5-bis(a,a,a-trifluro-p-tolyl)-1,4-pentadien-3-one	

CL 243049	p-toluic acid methyl ester, a,a,a -trifluro	
CL 243236-Me	cinnamic acid, p-trifluromethyl methyl ester	
CL 89466	2-one-1,4,5,6-tetrahydro-5,5-dimethyl pyrimidine	

Attachment 2: Standard Assumptions and PHED Surrogate Tables; Occupational and Non-Occupational Postapplication Exposure

Short-term Post Application Assessment for Hydramethylnon Treated Pineapple

Table 18. Exposure Inputs Summary			
Exposure Potential	Transfer Coefficients (cm2/hr) (1)		Activities (1)
	Used for RA	Range	
Very Low	N/A	N/A	N/A
Low	300	140 - 290	Irrigation, Scouting, Thinning, Weeding (hand)
Medium	500	364 - 1,908	Irrigation, Scouting
High	1000	364 - 1,908	Harvest (hand), Pruning (hand)
Very High	N/A	N/A	N/A

Table 19. Pineapple Worker Reentry MOE Estimates												
DAT (3)	DFR LEVELS (ug/cm2)		DOSE (mg/kg/day) (4)					MOEs (5)				
	Not Adjusted	Adjusted for Rate	Very Low	Low	Medium	High	Very High	Very Low	Low	Medium	High	Very High
0	0.049	0.049	N/A	1.7E-5	2.8E-5	5.6E-5	N/A	N/A	100000	60000	30000	N/A

Footnote:

1. Crop groupings and transfer coefficients from Science Advisory Council for Exposure: Policy Memo #003.1 'Agricultural Transfer Coefficients', August 17, 2000.
2. Maximum label rates from end use product labels.
3. DAT = Days after treatment; DAT0 = On the day of treatment, after sprays have dried; assumed approximately 12 hours.
4. The absorbed dermal dose = DFR (ug/cm2) x TC (cm2/hr) x conversion factor (1 mg/1,000 ug) x exposure time (hrs) x dermal absorption / body weight (kg).
5. MOE = Dermal toxicity endpoint (mg/kg-day)/absorbed dermal dose (mg/kg-d).

Occupational Exposure Assumptions & Data Sources

Area Treated

The amount of acres treated per day for each handler scenario was based on ExpoSac Policy #9 (7/5/00). Professional lawn care operators (LCOs) were assumed to treat 1 acre per day for hand and belly grinder applications. It was assumed that LCOs using push type spreaders will treat 5 acres per day.

Unit Exposures

The unit exposures used for bare hands and the belly grinder scenarios are based on the PHED version 1.1. as presented in the August 1998 PHED Surrogate Exposure Guide. Additional information regarding the use of PHED is included in Appendix B of this assessment (i.e. policy for its use, number of replicates, data grade, and data confidence levels).

The LCO unit exposure is also based on an ORETF study (ORETF Study No. OMA001 -- Exposure of Professional Lawn Care Workers During the Mixing, Loading, and Application of Granular Turf Pesticides Utilizing a Surrogate Compound). This ORETF study is based on a surrogate compound, dacthal, and contains 20 replicates of test subjects wearing chemical resistant gloves and 20 replicates of test subjects wearing no gloves. This study monitored test subjects applying a granular product packaged in 50 pound bags using a LESCO push rotary spreader. Various passive dosimetry techniques were employed to estimate both long pants and long sleeved shirts as well as short pants and short sleeved shirts. The geometric mean of dermal unit exposures (0.31 mg/lb ai handled) was selected for this risk assessment.

Personal Protective Equipment Level (PPE)

The baseline level of PPE for LCOs was assumed to be single layer clothing, no gloves and no respirator.

Non-Occupational Exposure Estimates: Formulae and Assumptions

This first formula illustrates the method of calculating granular ingestion by children (SOP 2.3.1):

PDR = IgR x F x CF1

where:

PDR = potential dose rate (mg/day)
IgR = ingestion rate of granular formulation (g/day)
F = fraction of ai in dry formulation (unitless)
CF1 = weight unit conversion factor to convert grams to milligrams (1000 mg/g)

It is assumed in the Residential SOP that a maximum of 0.3 gm/day dry pesticide will be ingested by young children. This is based on an application rate of 150 lb formulated product to a half acre. The amount of product per square foot would be approximately 3 g/ft^2, and a child is assumed to consume one-tenth of the product available in a square foot. This is believed to be an upper-percentile estimate. Since hydramethylnon labels vary from 1-3 lb formulated product per acre, the maximum ingestible granules was adjusted to 0.003 grams/day (3 milligrams). The fraction of ai in granular formulations of hydramethylnon varies from 0.03% to 1%.

The following demonstrates the method used to calculate exposures that are attributable to a child touching treated turf and then putting their hands in their mouth (SOP 2.3.2, revised 2000). For the granular postapplication exposure estimate, the DFR is replaced by the experimentally determined transfer rate:

$$PDR = (DFR * EF * SA * Freq * Hr * (1mg/1000\mu g))$$

where:

PDR = potential dose rate (mg/day)
DFR(t) = (for sprayed turf) Dislodgeable Residue (5%) on day of treatment (µg/cm^2); (for granular application) 1.1% of application rate for moist hands;
EF = saliva extraction factor of 50% of total DFR;
SA = surface area of two fingers (cm^2);
Freq = frequency of hand-to-mouth events (events/hour); and
Hr = exposure duration (hours).

As indicated above, the dislodgeable foliar residue represents the amount of pesticide that can be removed from turf by the (potentially wet) hands of a child, while the turf transferable residue represents the amount of chemical on the surfaces of treated leaves that can rub off on dry skin or clothing. The methodology used to obtain a TTR value could underestimate incidental oral exposures to children. The TTR data are designed to assess dermal exposure to pesticides using the

choreographed activity Jazzercise, measured on dry cotton dosimeters, and do not address the transferability of residues by hands wetted with saliva. The 5% transfer factor is based on data by Clothier (1999), which supports the standard value of 5% of the applied rate being dislodgeable residue as cited in the revised Residential SOPs (2/01). The surface area for 1-3 fingers used (20 cm^2) is the median surface area for a toddler (age 3 years) as updated by the SAP meeting in 1999. The frequency of hand-to-mouth events is 20 events per hour as updated in the 1999 SAP meeting. The 2 hour duration value is a recommended value from the U.S. EPA Exposure Factors Handbook. This model for hand-to-mouth dose is based on the premise that a child puts 2-3 fingers in their mouths, 50% of the residues on the hands are transferred from the hands to the mouth (Extraction Factor), and that all of the dislodgeable residues available on the treated turf transfer to the child's hand each time they exhibit this behavior.

The following illustrates the approach used to calculate exposures that are attributable to a object-to-mouth exposure scenario, such as a child mouthing treated turf (SOP 2.3.3, revised 2000):

$$PDR = (DFR * IgR * (1mg/1000\mu g))$$

where:

PDR = potential dose rate (mg/day);

DFR(t) = Dislodgeable Foliar Residue (DFR) at time (t) where the longest duration (t) is dictated by the kinetics observed in the TTR study ($\mu g/cm^2$);

IgR = ingestion rate for mouthing of grass (or other object) per day (cm^2/day).

Lacking DFR data for hydramethylnon on turf, such as would be dislodged by an object mouthed by a child, the Agency chose to use the standard assumptions in the updated Residential SOPs, normalized for lbs ai/acre applied. It is assumed that 5% of the applied rate (2 lb ai/A) is available for ingestion after being mouthed. The ingestion rate used (25 cm^2/day) assumes that a child will grab a handful of turf, or a small object, mouth it and remove all dislodgeable atrazine residues, and then remove it from their mouth as described in the Residential SOPs. The standard time period is 2 hours, as explained above. The surface area of (25 cm^2/day) is thought to approximate a handful of turf or a small object that is mouthed.

Incidental Soil Ingestion:

$$PDR = (SR_t * IgR * CF1)$$

where:

PDR = potential dose rate (mg/day)

SR_t = soil residue on day "t" ($\mu g/g$), assuming average day of reentry "t" is day 0

IgR = ingestion rate of soil (mg/day), assumed to be 100 mg/day

CF1 = weight unit conversion factor to convert the µg of residues on the soil to grams to provide units of mg/day (1E-6 g/µg)

and

$$SR_t = AR * F * (1-D)^t * CF2 * CF3 * CF4$$

where:

AR = application rate (lb ai/acre)
F = fraction of ai available in uppermost cm of soil (fraction/cm), assumed to be 100 percent based on soil incorporation into top 1 cm of soil after application
D = fraction of residue that dissipates daily (unitless)
t = postapplication day on which exposure is being assessed
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to µg for the soil residue value (4.54×10^8 µg/lb)
CF3 = area unit conversion factor to convert the surface area units (ft^2) in the application rate to cm^2 for the SR value (2.47×10^{-8} acre/cm^2 if the application rate is per acre)
CF4 = volume to weight unit conversion factor to convert the volume units (cm^3) to weight units for the SR value (0.67 cm^3/g soil)[7]
t = postapplication day on which exposure is being assessed, assumed to be day zero

The following specific assumptions and factors were used in order to complete this exposure assessment:

- The application rate was 0.02 lb ai/acre
- The amount of residue available on day zero for dermal contact is 5% of the application rate, except for wet-hand transfer, which is assumed to be 20%.
- For short-term exposure, the dermal transfer coefficient for adults and children is 14,500 and 5,200 cm^2/hour, respectively. For intermediate-term exposure, the dermal transfer coefficient for adults and children is 7,300 and 2,600 cm^2/hour, respectively.
- The exposure time is assumed to be 2 hours for adults and children.
- Due to a lack of scenario-specific exposure data, HED has calculated exposure values for adults using surrogate dermal transfer coefficients that represent activities such as mowing, golfing, and yard work. Most of the transfer coefficients used are based on data submitted by the ARTF and ORETF and are reflected in the revised HED exposure guidance Policy 3.1 (8/2000).
- Adults were assumed to weigh 70 kg for the short-term postapplication dermal dose estimate. Young children and toddlers are represented by a 15 kg 3 year old, as recommended in the Residential SOPs.

PHED DATA QUALITY FOR OCCUPATIONAL / RESIDENTIAL HANDLER SCENARIOS

Loading Granular Formulations	PHED V1.1	350 acres for general Ag aviation; 80 acres for sod farms and 40 acres for golf course turf	**Baseline:** Hand (10 replicates) exposure values are based on all grade data, dermal (33-78) exposure values are based on ABC grade data , and inhalation (58 replicates) exposure values are based on AB grade data. Low confidence in hand/dermal data, and high confidence in inhalation data. No protection factor was needed to define the unit exposure value. **PPE:** The same inhalation data are used as for the baseline coupled with an 80% protection factor to account for the use of a dust/mist respirator. Hand (45 replicates) and double layer (12-59 replicates) exposure values are based on ABC grade data. Medium confidence in baseline + gloves data; low confidence in double layer + gloves data. . **Engineering Controls (Lock 'n Load):** The same data are used as for baseline coupled with a 98% protection factor to account for Lock 'n Load.
Applying Granular Products by Airplane	PHED V1.1	350 acres for general Ag aviation; sod may be less	
Applying with a Tractor Drawn Spreader	PHED V1.1	200 (high acreage crop), 80 and 40 acres (golf course) Fertilizer: commercial 320 acres; private 160 acres	**Baseline:** Dermal (1-5 replicates); hand (5 replicates); and inhalation (5 replicates) exposure values are all based on AB grade data. Low confidence in the unit exposure values. No protection factors were needed to define the unit exposure values. **PPE:** The same dermal and inhalation data are used as for the baseline coupled, when needed, with a 50% protection factor to account for an additional layer of clothing and an80% protection factor to account for the use of a dust/mist respirator. Gloved-hand (0 replicates) exposure value is low confidence due to lack of data. **Engineering Controls: (enclosed cab):** Dermal (2-30 replicates), hand (24 replicates), and inhalation (37 replicates) exposure values are based on AB grade data. High confidence in the dermal unit exposure value. Low confidence in inhalation unit exposure value. No protection factors were needed to define the unit exposure value.
Loading and Applying Granulars with a Push Type Spreader (LCO)	ORETF Study OMA001	5 acres	**Baseline**: Hand (20 ungloved replicates), dermal (40 replicates) and inhalation (40 replicates) data were used to establish unit exposure values. **PPE**: The same dermal and inhalation data are used as for the baseline coupled, when needed, with a 50% protection factor to account for an additional layer of clothing and a 80% protection factor to account for the use of a dust/mist respirator. Gloved-hand (20 replicates) data used to establish exposure value. **Engineering Controls**: Not available for this scenario.

Granulars with a Bellygrinder (LCO / PCO / Resident)	PHED V1.1	1 acre for spot treatments to turf	**Baseline:** Dermal (29-45 replicates); hand (23 replicates) exposure values based on ABC grade data. Inhalation (40 replicates) exposure value is based on AB grade data. Medium confidence in dermal/hand data and high confidence in the inhalation unit exposure value. No protection factors were needed to define the unit exposure values. **PPE:** The same dermal and inhalation data are used as for the baseline coupled, when needed, with a 50% protection factor to account for an additional layer of clothing and a 80% protection factor to account for the use of a dust/mist respirator. Gloved-hand (20 replicates) exposure value is based on all grade data. Low confidence in gloved hand data. **Engineering Controls:** Not available for this scenario.
Applying Granular products by Hand (LCO / PCO / Resident)	PHED V1.1	1000 ft2	**Shorts, Short sleeved shirt:** Dermal replicates = 16, ABC grade. Hand replicates = 0. **Low Confidence** due to lack of "no glove" replicates for this use scenario. The only way to estimate "no glove" hand exposure is to back-calculate from the gloved estimate. **Long-sleeved Shirt, Long Pants**: Dermal replicates = 16, ABC grade. Hand replicates = 0. **Low Confidence** due to lack of "no glove" replicates for this use scenario. The only way to estimate "no glove" hand exposure is to back-calculate from the gloved estimate. **Single Layer Clothes with Gloves**: Dermal replicates = 16, ABC grade. Hand replicates = 15, ABC grade. **Medium Confidence** **Inhalation:** 16 replicates, ABC grade. **Medium Confidence** **NOTE**: This scenario is representative of a granular bait dispersed by hand as these data were generated by test subjects applying a granular bait by hand around driveways in a residential setting. The significant issue that should be considered when using these data is that the individuals wore gloves during the process and it is unlikely that most homeowners will wear gloves. Hence, an adjustment of the hand exposure data was required using a theoretical protection factor to quantify bare hand exposure scenarios.

Description of the Pesticide Handler Exposure Database (PHED)

It is the policy of HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 2/18/99)

PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides are primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, ground-boom), and clothing scenarios (e.g., gloves, double layer clothing).

Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (e.g., chest upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body.

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure assessments.

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposures. These include administrative controls, the use of personal protective equipment or PPE, and the use of engineering controls. Occupational handler exposure assessments were completed by HED using baseline, PPE, and engineering controls. [Note: Administrative controls available generally involve altering application rates for handler exposure scenarios. These are typically not utilized for completing handler exposure assessments.] The baseline clothing/PPE level scenario for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical-resistant gloves, and no respirator. The first level of mitigation generally applied is PPE. As reflected in the calculations included herein, PPE may involve the use of an additional layer of clothing, chemical-resistant gloves, and a respirator. The next level of mitigation considered in the risk assessment process is the use of appropriate engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include closed tractor cabs, closed mixing/loading/transfer systems, and water-soluble packets.